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Condidit: **Gunnar Dahlberg** †

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DIE FERTILITÄT IM BLUTERSTAMM VON TENNA (HÄMOPHILIE B)

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Einleitung

Für die Bestimmung menschlicher Mutationsraten gibt es zwei prinzipiell verschiedene Methoden; eine direkte und eine indirekte.

Mit der *direkten Methode* können nur dominante Gene erfaßt werden. Alle neu auftretenden, sogenannt sporadischen Fälle, werden ausgezählt und ergeben durch die doppelte Zahl aller Geburten dividiert, die Mutationsrate.

Der *indirekten Methode* liegt die Überlegung zugrunde, daß Merkmale, die einen Fortpflanzungsnachteil bewirken, längst verschwunden sein müßten, wenn der Nachteil des Gens nicht durch ständige Neumutanten kompensiert würde. Es geht also hier darum, die Verlustrate eines Gens möglichst genau zu ermitteln. Dies gelingt nur, wenn die Häufigkeit (x) und die Fortpflanzungseignung (f) der Merkmalsträger bestimmt werden können. Pro Generation muß dann mit einem Verlust von $N \cdot x \cdot (1-f)$ Merkmalsträgern gerechnet werden. Bei autosomal rezessivem Erbgang wird dieser Selektionsverlust durch eine Mutationsrate von $u = x \cdot (1-f)$ wieder ausgeglichen.

Für die *Hämophilie* mit ihrem rezessiv geschlechtsgekoppelten Erbgang trifft die Selektion praktisch nur das männliche Geschlecht. Da aber die Männer nur $\frac{1}{3}$ aller X-Chromosomen tragen, wird der Genverlust und damit die Mutationsrate mit $u = \frac{1}{3} x \cdot (1-f)$ berechnet. Diese von *Haldane* (1935) aufgestellte Formel setzt voraus, daß der gesamte Genverlust durch Neu-

mutanten kompensiert werde. Für die andere Möglichkeit einer Ausgleichung durch eine erhöhte Fertilität der heterozygoten Frauen findet *Haldane* keine Anhaltspunkte.

Für die von *Andreassen* zusammengestellten dänischen Bluter bestimmte *Haldane* (1947) eine Fortpflanzungseignung von f = 0,286 und eine Mutationsrate von 3,6 · 10⁻⁵. *Vogel* (1955) hat für die von Fonio publizierten Schweizer Bluter f = 0,386 berechnet und eine Mutationsrate von 2,2 · 10⁻⁵ erhalten.

Seitdem durch *Koller* et al. (1950), *Biggs* et al. (1952) und eine Reihe anderer Forscher gezeigt wurde, daß es zwei Typen von geschlechtsgekoppelter Hämophilie gibt, Hämophilie A und Hämophilie B, muß die Frage nach den Mutationsraten für die beiden Typen getrennt wieder aufgenommen werden.

Für den Bluterstamm von Tenna bietet die sehr eingehende Arbeit von *Moor-Jankowski*, *Truog* und *Huser* (1957) die Möglichkeit, neue Berechnungen über die Fortpflanzungseignung anzustellen. Alle 10 serologisch untersuchten Bluter aus verschiedenen Zweigen dieses Stammes gehören zur Hämophilie B (*Moor-Jankowski*, *Huser* und *Geiger*, 1957). Der ganze Stamm kann deshalb zu diesem Hämophilietyp gerechnet werden, der in verschiedenen Ländern zu 10%–20% vertreten ist (*Ottolander* 1955).

A. Das Material

Das Material der Arbeit von *Moor-Jankowski*, *Truog* und *Huser* (1957) über den Tenner Bluter-Stamm ist in einer dreiteiligen Nachfahrentafel niedergelegt. Es umfaßt in 11 Generationen 3068 Nachkommen der Eltern des ersten bekannten Bluters von Tenna, der von 1676–1741 gelebt hat. In Teil A sind die Nachkommen einer Schwester dargestellt, bei der offenbar das Gen nicht vorhanden war oder nicht weitergegeben wurde. Dieser Teil der Nachfahrentafel ist mit Ausnahme eines sporadischen Bluters vollständig frei von Hämophilie, umfaßt aber Personen, die an den gleichen Orten lebten, gleiche Berufe und Lebensgewohnheiten hatten wie die Bluter und deren nächste Verwandte, also eine normale Bevölkerung, die zum Vergleich bestens geeignet ist. Teil B enthält die direkten Nachkommen des ersten Bluters und Teil C diejenigen einer Schwester, die das Blutergen weitervererbt hat. Wegen der fast lückenlosen Einbeziehung aller Nachfahren und der genauen Eintragung aller, auch der früh verstorbenen Kinder, sind die Bluterfamilien unabhängig von ihrer Größe und von der Zahl der Bluter gleichmäßig erfaßt worden. Die für die Aufnahme einzelner Familien charakteristischen Auslesefehler spielen somit bei diesem

Material keine Rolle. Der erste Bluter (in der Generation III der Nachfahrentafel) mit seinen 11 Kindern wurde aber für die Fertilitätsberechnungen vorsichtshalber weggelassen, denn er ist der Vorfahre von insgesamt 25 Blutern, wovon 10 noch am Leben sind. Ohne diesen Teil wäre der Stammbaum möglicherweise nicht bearbeitet worden.

Die nachfolgend aufgeführten Zahlen sind der Monographie (*Moor-Jankowski*, *Truog* und *Huser* 1957) entnommen, unter Beiziehung des nicht veröffentlichten Namensverzeichnisses, das in mehreren Exemplaren an verschiedenen, in der Monographie verzeichneten Stellen deponiert ist.

B. Die Fortpflanzungsgröße der Bluter

1. Der zeitliche Beginn der Manifestation bei den Tenner Hämophilen

Von den 43 verstorbenen Blutern ist der jüngst verstorbene 3 Jahre alt geworden, während in der Vergleichsbevölkerung 21% der Kinder vor und mit 3 Jahren starben (Monographie Tab. 13 und Fig. 3). Schon diese Zusammenstellung zeigt, daß die *Bluter des Tenner Stammes vor dem 3. Lebensjahr meistens nicht erkannt werden können*. Dies geht vor allem auch aus dem genaueren Studium der Einzelfälle hervor. Es hat sich gezeigt, daß erst nach 6 Jahren mit ziemlicher Sicherheit gesagt werden kann, ob ein Knabe Bluter ist oder nicht.

Wenn die durchschnittliche Kinderzahl der Bluter berechnet werden soll, so müssen dabei *alle* genetischen Bluter, nicht nur die manifesten erfaßt werden. Es fragt sich also, mit wievielen frühverstorbenen, noch nicht manifesten Blutern im Stamm von Tenna gerechnet werden muß. Um hierfür einen brauchbaren Schätzungswert zu erhalten, wurde für alle vor dem 3. Lebensjahr verstorbenen Knaben der IV. bis X. Generation berechnet, mit welcher Wahrscheinlichkeit das Blutergen vorhanden gewesen sein mußte.[1] Nach dieser Berechnung haben von den 32 früh verstorbenen möglichen Blutern 10,5 das Gen getragen.

Außer diesen 32 enthält die Nachfahrentafel noch 5 Knaben, die in folgendem Alter starben: 3, 3, 4, 5, 6 Jahre. Die 4 ersten haben das Gen mit einer Wahrscheinlichkeit von je 50% getragen, der letzte mit 25%. Diese 5 Knaben wurden aber alle als gesund gewertet, weil andererseits 6 manifeste Bluterknaben im Alter von 3, 4, 5, 5, 6, 6 Jahren gestorben sind und natürlich als Bluter gezählt wurden. Ohne Kenntnisse darüber, daß sie Bluter waren, wären 5 von diesen mit 50% und einer mit 6% als Bluter berechnet worden. In Tab. 1 sind die Standortnummern all dieser Fälle aufgeführt.

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[1] Die Berechnungsweise ist von *S. Rosin* in der Monographie (*Moor-Jankowski* et al. 1957) ausführlich dargestellt worden.

Tabelle 1

Standortnummern der vor 6 Jahren gestorbenen, genetisch möglichen Bluter
der Generationen IV–X.

Location numbers of genetically possible bleeders dead before the age of 6.

	Gene-ration	Sterbealter Jahre		Age of death		
		0–2	3	4	5	6
ohne	IV			29	34	
Manifestation	V	14, 19, 22, 66, 70, 72, 80	47			
von	VI	69, 74, 75, 79, 90, 122, 126				
Hämophilie	VII	123, 131, 132, 195				
	VIII	(174), 191, 222, 234, 269,			(163)	235
without		270, 319, 320, (339)				
manifestation	IX	328, 329, 379, 386	410a			
of hemophilia	X	486				
manifest			VI 99	VII 208	IV 24	IV 30
Hämophile					VIII 268	VI 102

Eingeklammerte Standortnummern: Die Wahrscheinlichkeit dafür, daß das Hämophilie-
gen vorhanden war, ist $<1\%$.

Location numbers in brackets: The probability that the hemophilia gene was pre-
sent is $<1\%$.

Es ist also damit zu rechnen, daß *11 Bluter ohne Manifestierung als
Kleinkinder gestorben* sind. Diese müssen in die folgenden Berechnungen
einbezogen werden.

Tabelle 2

Männliche Nachkommen im Tenner Stamm. IV.–X. Generation

Male descendants of the Tenna kindred

	Total	ledig unmarried		verhei-ratet married	Zahl der Kinder									Number of children	
		$\leqq$6.J.	>6J.		0	1	2	3	4	5	6	7	8	Total	Durchschnitt Mean
Bluter Bleeders	53*	17*	19	17	1	4	2	3	2	1	3	0	1	56	1,057 $\pm$0,275
Teil A Part A	153	23	45	85	11	7	20	15	14	8	6	2	2	254	1,660 $\pm$0,169

* Davon 11 berechnete, nicht manifeste Bluter.
  Eleven of whom are calculated to be bleeders but are not known as such.

2. Die durchschnittliche Kinderzahl der Bluter
im Vergleich mit derjenigen der männlichen Nachkommen aus Teil A

Aus Tab. 6 und Tab. 8 der Monographie kann unter Einbeziehung der frühverstorbenen, nicht manifestierten Bluter folgende Zusammenstellung gewonnen werden (Tab. 2).

Die *Fortpflanzungseignung der Bluter von Tenna* wird somit

$$f = 0{,}64 \pm 0{,}18.$$

Die angegebene Streuung berechnet sich aus: $f = \dfrac{x}{y}$; $V(f) = f^2 \left[\dfrac{V(x)}{x^2} + \dfrac{V(y)}{y^2} \right]$. Weil die Verteilung der Kinderzahl sehr einseitig ist (große 0-Klasse) ist wohl die Streuungsangabe für f nicht sehr genau. Für das von Vogel (1955) berechnete $f = 0{,}386$ für alle Hämophilen der Schweiz wird die zugehörige Streuung etwa 0,10 betragen.

3. Die Komponenten der Fortpflanzungseignung der Bluter

Die Fortpflanzungseignung ist das Produkt aus der relativen Verheiratungsziffer und der relativen Kinderzahl pro verheiratete Person. Für

Tabelle 3

Die Komponenten der Fortpflanzungseignung der Bluter

The relative fitness of hemophiliacs and its components

	Vergleichsbevölkerung (Teil A) Normal population (Part A)	Bluter Bleeders	Bluter relativ zur Vergleichsbevölkerung Bleeders related to non-bleeders
Überleben des 6. Jahres Dead after 6 years of life	85%	68%	0,80
Mittleres Lebensalter Mean duration of life	41,3 J.	22,0 J.	0,53
Verheiratungsziffer Married	55,5%	32,1%	0,58
Mittlere Kinderzahl der verheirateten Männer Mean number of children of married men	3,0	3,3	1,10
Mittlere Kinderzahl aller männlichen Personen Mean number of children of all male persons	1,66	1,06	f = 0,64

die Verheiratungsziffer spielt unter anderem das mittlere Lebensalter eine Rolle, das stark von der Kindersterblichkeit abhängt. Diese Größen sind in Tab. 3 wiedergegeben und stützen sich mit Ausnahme des mittleren Lebensalters auf Tab. 2 (Sterbealter aus Monographie, Fig. 3).

Die Tab. 3 zeigt, daß die Kindersterblichkeit im Tenner Bluterstamm nicht sehr groß ist und daß die Bluter, die sich verheiratet haben, nicht etwa weniger, sondern eher etwas mehr Nachkommen haben als die Nichtbluter. Obschon sich unser Material auf die Zeitspanne von 1700–1950 bezieht, also in eine Zeit mit geringerer Lebenserwartung zurückreicht, ist *das mittlere Lebensalter der Bluter von 22 Jahren wesentlich höher als dasjenige aus dem dänischen Gesamtmaterial von Andreassen.*

Im Gesamten zeigt sich, daß die Fortpflanzungseinbuße (1–f) der Hämophilie B im Tenner Stamm bedeutend geringer ist als bei den bisher untersuchten heterogenen Hämophilen Dänemarks und der Schweiz.

C. Die Fortpflanzungseignung der Konduktorinnen

Die Gesamtheit der Konduktorinnen und die Zahl ihrer Kinder kann nicht direkt ausgezählt werden, weil ja von vielen weiblichen Nachfahren nicht bekannt ist, ob sie das Blutergen erhalten haben oder nicht. Es bestehen jedoch drei Möglichkeiten, über diese Größen Aufschluß zu erhalten.

1. Die Kinderzahl aller weiblichen Nachkommen in den Bluterlinien der Teile B und C, die viele Konduktorinnen enthalten, kann mit derjenigen der weiblichen Nachkommen aus Teil A verglichen werden. Daraus ergibt sich aber nur eine Mindestabweichung für die Fortpflanzungseignung der Konduktorinnen vom Normalwert, weil in den Teilen B und C ja auch erbgesunde Töchter und Frauen mitgezählt wurden.

2. Alle Töchter von Blutern sind unabhängig von ihren Kindern als Konduktorinnen zu bezeichnen.

3. Die Blutermütter stellen eine spezielle Auslese der Konduktorinnen dar. Unter Berücksichtigung der Auslesefehler kann auch aus dieser Gruppe die Fortpflanzungsgröße bestimmt werden.

1. Die weiblichen Nachkommen und deren Kinder in den Hämophiliezweigen der Teile B und C und im hämophiliefreien Teil A des Tenner Stammes

Aus den Tabellen 10 und 11 der Monographie kann folgende Tabelle zusammengestellt werden (Tab. 4):

Tabelle 4

Weibliche Nachkommen der Generationen V–Xa und deren Kinder

Female descendants of generations V–Xa and their children

	Total	ledig unmarried	verheiratet married	Zahl der Kinder — Number of children															Total	Durchschnitt Mean
				0	1	2	3	4	5	6	7	8	9	10	11	12	13		
Teile B + C Parts	110	45 40,9%	65 59,1%	8	5	12	11	10	3	5	2	5	1	1	0	1	1	245	$2,227 \pm 0,279$
Teil A Part A	139	44 31,6%	95 68,4%	13	9	21	13	18	10	5	3	3	0	0	0	0	0	287	$2,065 \pm 0,188$
																			$g_1 = 1,08$

Tabelle 7

Blutertöchter und ihre Kinder

Daughters of bleeders and their children

Generation	Blutertöchter — Daughters of bleeders			Zahl ihrer Kinder — Number of their children									total	Durchschnitt Mean
	Total	ledig unmarried	verheiratet married	0	1	2	3	4	5	6	…	13	total	
IV	6	0	6	1				1	2	2			26	4,3
VI	4	0	4			1	1	1	1				14	3,5
VIII	13	6	7			4		1		1		1	31	2,4
IX	3	1	2	1			1						3	} 1,3
X	2	1	1			1							2	}
XI	1	0	1				1						3	}
IV–XI	29	8	21	2	0	6	3	3	3	3		1	79	$2,724 \pm 0,539$

Weil in den hier benützten Familien der Teile B + C nicht alle weiblichen Nachkommen Konduktorinnen sind, erhalten wir für deren Fortpflanzungseignung nur einen Mindestwert; also $g_1 > 1{,}08$. Die beiden Durchschnittswerte sind aber längst nicht gesichert voneinander verschieden, so daß hier höchstens ein Hinweis für eine erhöhte Kinderzahl der Konduktorinnen vorliegt.

Folgende Analyse der Verteilung der Kinderzahlen kann aber einen weiteren Beitrag zu dieser Frage liefern: Zunächst kann festgestellt werden, daß die Streuung in Teil B + C mit $s^2 = 8{,}56$ wesentlich größer ist als diejenige in Teil A mit $s^2 = 4{,}89$. ($F = 1{,}75$; $n_1 = 109$; $n_2 = 138$; $P < 1\%$.) Diese Feststellung, daß die Kinderzahlen im Hämophilieteil des Stammbaumes anders verteilt sind, kann aber noch durch die Analyse der speziellen Form der Verteilung erhärtet werden:

Für Teil A verteilen sich die Häufigkeiten der Kinderzahlen nach dem *Poisson*schen Gesetz, wenn die kinderlosen Familien nicht mitberücksichtigt werden.

Der Ausschluß der 0-Klasse läßt sich rechtfertigen, da für alle Familien mit Kindern die prinzipielle Fertilität beider Eltern erwiesen ist, während die kinderlosen Ehen fertile und sterile Partner in allen 4 Kombinationsmöglichkeiten umfassen können.

Die Berechnung der *Poisson*-Verteilung erfolgt am besten nach folgenden Formeln:

$$\varphi(x+1) = \frac{\lambda}{x+1} \cdot \varphi(x)$$

$$\varphi(o) = e^{-\lambda} \qquad \text{(Linder 1951, S. 147)}$$

Für die abgeschnittene und der Gesamtzahl angepaßte Verteilung wird

$$\lambda = \overline{x} = \frac{287}{82 + a} \qquad \text{wobei a die unbekannte Zahl der 0-Gruppe darstellt}$$

$$\text{also } a = (82 + a) \cdot e^{-\overline{x}}$$

$$\text{daraus wird } \overline{x} = 3{,}500(1 - e^{-\overline{x}}) \text{ und}$$

$$\lambda = \overline{x} = 3{,}381; \quad a = 2{,}888$$

Damit kann für jede Kinderzahl x die Zahl der zu erwartenden Familien $N \cdot \varphi(x)$ berechnet und mit der beobachteten Zahl $f(x)$ verglichen werden. Mit dem χ^2-Text kann dann die Abweichung der beobachteten Zahlenreihe von der erwarteten *Poisson*-Reihe geprüft werden. (Tab. 5 und Abb. 1)

Die beobachteten Werte stimmen also mit einer *Poisson*-Verteilung sehr gut überein. Die Abweichungen liegen nicht systematisch.

Die gleiche Rechnung ergibt für die Teile B+C folgende Werte: (Tab. 6 und Abb. 1)
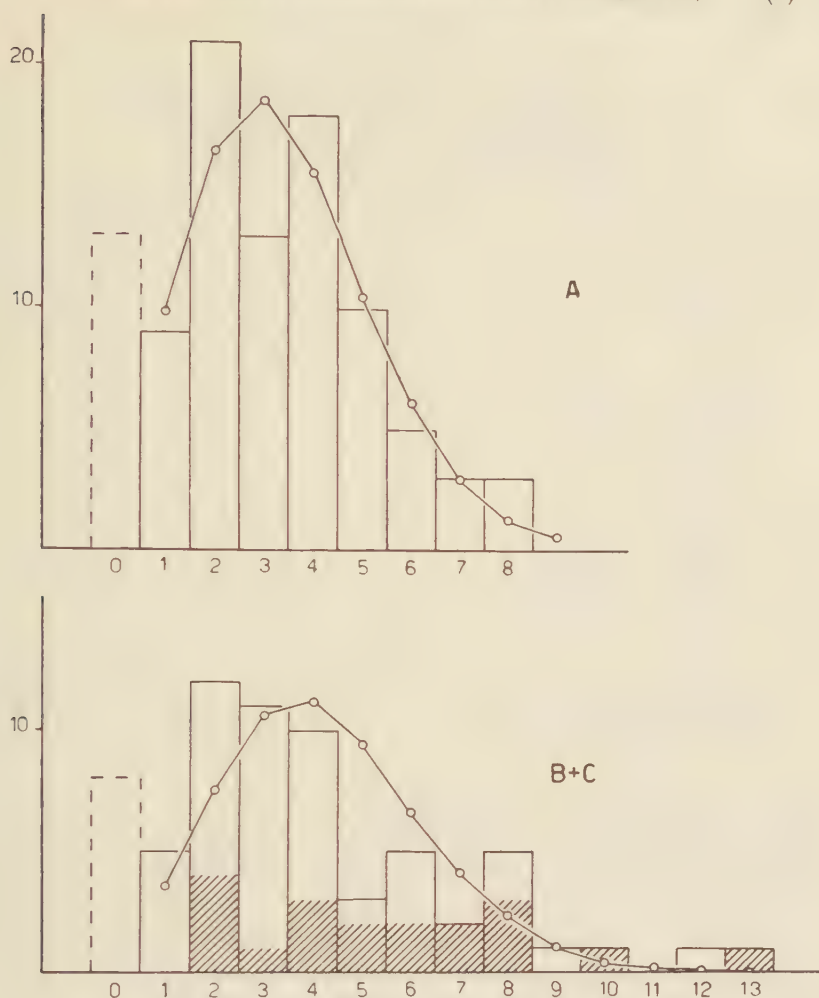
Abb. 1. Verteilung der Kinderzahl der verheirateten weiblichen Nachkommen aus
Teil A und Teil B + C.

Abszisse:	Zahl der Kinder
Ordinate:	Zahl der Frauen
Polygon:	Angepaßte, abgeschnittene *Poisson*sche Verteilung
schraffiert:	Mütter mit Blutern unter den beiden ersten Kindern

Distribution of the number of children of married female descendants from part A
and from part B + C.

Abscissa:	number of children
Ordinate:	number of women
Polygon:	the fitted truncated Poisson distributions
hatched area:	mothers having bleeders among their two first born children.

Tabelle 5

Kinderzahlen der Mütter aus Teil A
verglichen mit einer abgeschnittenen *Poisson*-Verteilung

Number of children of mothers from part A
compared with a truncated *Poisson*-distribution

x	f (x)	N · φ (x)	d	χ^2
0	(2,89)	(2,89)	0	0
1	9	9,76	—0,76	0,06
2	21	16,51	+4,49	1,22
3	13	18,60	—5,60	1,69
4	18	15,72	+2,28	0,33
5	10	10,63	—0,63	0,04
6	5	5,99	—0,99	0,16
7	3			
8	3	4,79	+1,21	0,31
Mehr	0			
Total	84,89	84,89	0	3,81

$\chi^2 = 3,81$ n = 5   P = 55%

x	Zahl der Kinder Number of children	N·φ (x):	Erwartete Zahl solcher Familien Expected number of such families
f(x):	Beobachtete Zahl von Familien mit x Kindern Observed number of families with x children	d:	Differenz Difference

Die Abweichung von der passendsten *Poisson*-Verteilung ist hier schwach gesichert. Da am Anfang und am Schluß zu viele, in der Mitte zu wenig Fälle beobachtet werden, machen diese Kinderzahlen den *Eindruck einer zusammengesetzten Verteilung. Neben einer Anzahl Mütter mit normal vielen Kindern ist eine Gruppe mit erhöhter Kinderzahl vorhanden. Daß* hierbei die Blutermütter einen über den durch Auslese nach einem Merkmal ihrer Kinder zu erwartenden Anteil ausmachen, soll unter 3 gezeigt werden.

2. Die Kinderzahl der Töchter von Blutern

Da in der Monographie eine entsprechende ausführliche Tabelle fehlt, sei sie hier wiedergegeben (Tab. 7, S. 7).

Die durchschnittliche Kinderzahl der Blutertöchter kann mit dem Durchschnittswert aus Teil A (Tab. 4: 2,065 ±0,188) verglichen werden und ergibt eine Fortpflanzungseignung dieser Gruppe von Konduktorinnen von

$$g_2 - 1,32$$

Der Wert dieses Vergleichs wird aber dadurch herabgesetzt, daß die

Tabelle 6

Kinderzahlen der Mütter aus den Teilen B und C
Vergleich mit der *Poisson*-Verteilung
Number of children of mothers from parts B and C
compared with a truncated *Poisson*-distribution

$\lambda = \overline{x} = \frac{245}{57+a}$ a = 0,837 $\overline{x}$ = 4,236

	f (x)	N · φ (x)	d	χ^2
0	(0,84)	(0,84)	0	0
1	5	3,55	+ 1,45	0,59
2	12	7,51	+ 4,49	2,68
3	11	10,60	+ 0,40	0,02
4	10	11,23	— 1,23	0,13
5	3	9,51	— 6,51	4,44
6	5	6,72	— 1,72	0,44
7	2	4,06	— 2,06	1,04
8	5	2,15	+ 2,85	3,77
9	1			
10	1			
11	0	1,67	+ 2,33	3,24
12	1			
13	1			
mehr	0			
Total	57,84	57,84	0	16,35

χ^2 = 16,35   n = 7   P = 2,2%

Bezeichnungen siehe Tabelle 5
For explanation see Table 5

Hauptzahl der Blutertöchter aus den Generationen IV–VIII stammen, während die Vergleichsbevölkerung zum größeren Teil aus den Generationen IX und X kommt. Vergleicht man die Generationen IV, VI und VIII der Blutertöchter (Generation V und VII enthalten keine) mit den Generationen V–VIII der Tafel A, so ergibt sich aber noch eine Erhöhung der Fortpflanzungseignung (Tab. 8).

Bis zur VIII. Generation zeigen also die als Töchter der Bluter gekennzeichneten Konduktorinnen eine 60% höhere Nachkommenzahl als die Vergleichsbevölkerung. Dieser beträchtliche Unterschied hat sicher für die spezielle Entwicklung des Tenner Bluterstammes eine bedeutende Rolle gespielt, darf aber nicht vorbehaltlos verallgemeinert werden, weil der kleinen Zahlen wegen keine statistische Signifikanz der Differenz besteht.

Tabelle 8

Vergleich der Blutertöchter (IV.–VIII. Generation) mit den Töchtern aus Teil A (V.–VIII. Generation)

Comparison of the daughters of bleeders with the daughters from part A

	Total	Töchter Daughters		Zahl der Kinder number of children											Total	Durchschnitt Mean
		ledig unmarried	verheiratet married	0	1	2	3	4	5	6	7	8	....	13		
Blutertöchter Daughters of bleeders	23	6	17	1	0	5	1	3	3	3	0	0		1	71	3,087 ± 0,644
Teil / part A	65	22	43	6	5	14	2	5	4	4	2	1		0	125	1,923 ± 0,279

$g_3 = 1,61$

Tabelle 9

Kinderzahl von Müttern mit Blutern unter den beiden erstgeborenen Kindern und der Mütter aus Teil A mit mindestens 2 Kindern

Number of children from mothers, having bleeders among their two first born children, and from mothers of part A with at least 2 children

	N	Zahl der Kinder Number of children											$\bar{x}$	s^2	$\frac{s^2}{\bar{x}}$
		2	3	4	5	6	7	8	9	10	....	13			
Blutermütter Mothers of bleeders	20	4	1	3	2	2	2	3	0	2		1	5,800	9,5368	0,4768
Mütter aus A Mothers from part A	73	21	13	18	10	5	3	3	0	0		0	3,808	2,7681	0,0379

$d = 1,992$ $s^2 d = 0,5147$
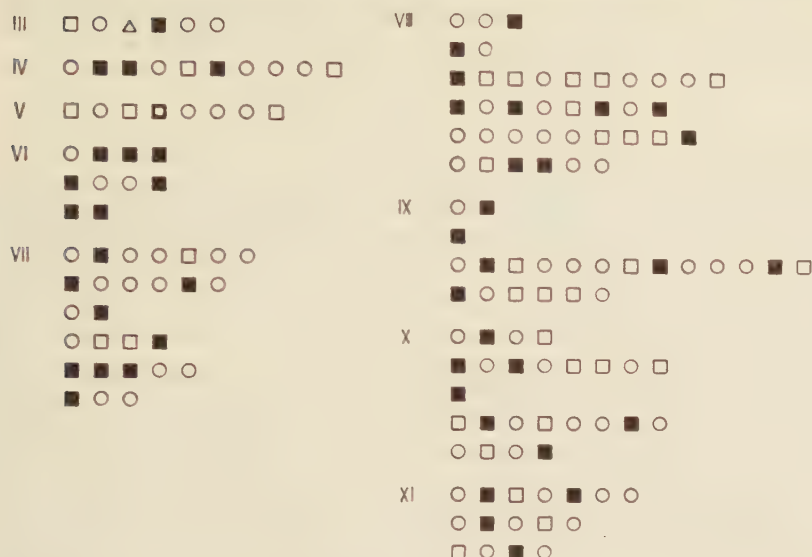
Abb. 2. Sämtliche Geschwisterschaften mit Blutern aus der Nachfahrentafel des Bluter-
stammes von Tenna (Monographie Tafel 5), geordnet nach Generationen und
Geburtsjahren.
ausgefüllte Quadrate: Bluter
V. 4:   mutmaßlicher Bluter (siehe Monographie)
XI: enthält nur Familien, bei welchen keine Kinder mehr zu erwarten sind.

All sibships containing bleeders from the descendant's table of hemophiliacs of
Tenna (Monography Tafel 5) recorded in sequence of generations and of birth.
black squares: bleeders
V. 4:   presumptive hemophiliac (cf. Monography)
XI: records only families in which no further children are expected.

Anders liegen die Dinge aber bei der viel größeren Streuung der Kinder-
zahlen der Blutertöchter: $s_1^2 = 9,54$; $s_2^2 = 5,07$; $F = 1,88$ und $P < 5\%$; der
Unterschied ist somit schwach gesichert. Hier zeigt sich also die gleiche
Erscheinung wie für die Teile B+C, wonach wahrscheinlich eine zusammen-
gesetzte Verteilung vorliegt.

3. Die Kinderzahl aller Konduktorinnen

Diese Größe ist vorerst nicht bestimmbar, weil eine ganze Anzahl von
Konduktorinnen weder durch ihre Nachkommen, noch durch ihre Vor-
fahren sicher als solche gekennzeichnet sind. Im Folgenden wird aber ver-
sucht, die Zahl aller Konduktorinnen und die Zahl ihrer Kinder mit Hilfe

des Anteiles der Mütter unter den weiblichen Nachkommen des Tenner Stammes und mit der Anzahl der Blutermütter zu bestimmen.

a. Die Kinderzahl der Blutermütter

Greifen wir alle Familien mit mindestens einem Bluter heraus, so haben wir damit eine Auslese getroffen, bei der die größeren Familien bevorzugt sind. Ein großer Teil der Konduktorinnen mit wenigen Kindern wird dabei nicht erfaßt, weil gerade kein Bluter darunter ist. Dieser Auslesefehler, der eine zu grosse Kinderzahl der Konduktorinnen vortäuscht, kann durch eine Gegenauslese behoben werden. Nehmen wir nur diejenigen Blutermütter, deren erstes Kind Bluter war, dann werden $\frac{1}{4}$ aller Konduktorinnen, die Mütter sind, erfaßt, und zwar unabhängig von ihrer Kinderzahl. (Die Wahrscheinlichkeit dafür, daß das Kind vom Vater das Y-Chromosom und von der Mutter das Blutergen bekommt, ist je $\frac{1}{2}$.) Die mittlere Kinderzahl dieser Gruppe kann mit der Kinderzahl aller Mütter der Normalbevölkerung verglichen werden. Wenn nun ferner alle Familien betrachtet werden, deren 1. Kind kein Bluter, aber deren 2. Kind ein Bluter war, so sind damit wiederum unabhängig von der Familiengröße für alle Familien mit 2 oder mehr Kindern weitere $\frac{3}{16}$ aller Familien mit Konduktorinnen, die Mütter sind, erfaßt worden. (Die Wahrscheinlichkeit dafür, daß das erste Kind gesund ist, ist $\frac{3}{4}$ und diejenige dafür, daß das zweite Kind Bluter ist, ist $\frac{1}{4}$.) Familien, bei denen der erste Bluter erst später aufgetreten ist, können analog behandelt werden. Hier sind sie nicht berücksichtigt, da sie wenig zur Information beitragen.

Nehmen wir alle Familien zusammen, bei denen entweder das erste oder erst das zweite Kind Bluter war, so sind damit $\frac{1}{4} + \frac{3}{16} = \frac{7}{16} = 44\%$ aller Konduktorinnen mit mindestens 2 Kindern erfaßt (oder aus $1-(\frac{3}{4})^2$, d.h. alle Familien, bei denen die beiden ersten Kinder nicht beide gesund sind). Für unser Material ergibt sich aus Abb. 2 folgende Zusammenstellung (Tab. 9):

Die Streuungen der beiden Verteilungen sind statistisch sehr gut gesichert verschieden:

$$F = \frac{9,54}{2,77} = 3,44 \qquad \begin{array}{l} n_1 = 19 \\ n_2 = 72 \end{array} \qquad P \ll 1\%$$

Unter dieser Voraussetzung darf die Differenz der Mittelwerte nicht mit dem üblichen t-Test geprüft werden. Nach *B.L.Welch* (siehe *Hald* 1952, S.397) ist folgendermaßen vorzugehen:

Die Differenz der Mittelwerte wird durch ihre Streuung dividiert:

$$d = 1,992$$

$$s^2_d = s^2_{\overline{x}_1} + s^2_{\overline{x}_2} = 0,5147$$

$$\frac{d}{s_d} = \frac{1,992}{\sqrt{0,5147}} = 2,78.$$ Zu diesem Wert kann aus der

t -Tafel der entsprechende P-Wert für n Freiheitsgrade entnommen werden, wobei n nicht wie üblich $N_1 + N_2 - 2$ ist, sondern wie folgt bestimmt wird:

$$\frac{1}{n} = \frac{c^2}{n_1} + \frac{(1-c)^2}{n_2} \quad \text{und} \quad c = \frac{s^2_{\overline{x}_1}}{s^2_{\overline{x}_1} + s^2_{\overline{x}_2}}.$$

Für unsern Fall mit $n_1 = 19$ und $n_2 = 72$ wird $n = 22$ und $P \sim 1\%$ d.h. *Bluttermütter mit mehr als 1 Kind haben gesichert mehr Kinder* als die entsprechenden Vergleichsmütter.

An der Erhöhung der Kinderzahl um 52% bei dieser Gruppe von Konduktorinnen sind aber nicht alle Blutermütter gleichmäßig beteiligt. Aus der gesicherten Streuungsvergrößerung geht vielmehr hervor, daß ein Teil der Mütter gerade beträchtlich mehr Kinder hat als die Vergleichsmütter, während die andern sich nicht abheben. Die für das viel größere, aber nicht rein aus Konduktorinnen bestehende Material aus Teil B+C (Seite 10) gefundene uneinheitliche Verteilung der Kinderzahlen wird also hier sehr deutlich und muß in dieser Gruppe von Konduktorinnen ihren Grund haben.

Diese Ergebnisse zeigen. daß sich das *Blutergen nicht direkt auf die Fruchtbarkeit der Konduktorinnen auswirkt*, wie dies *K. H. Bauer* (zit. nach *Schlößmann* 1930) angenommen hat. Das Auseinanderfallen der Verteilung in 2 Gruppen führt vielmehr zur Ansicht, daß *bei einem Teil der Mütter die schon vorhandenen oder doch zu erwartenden Verluste von Blutersöhnen durch eine Vermehrung der Kinderzahl kompensiert wird*. Die von *Bauer* und *Schlößmann* beobachtete Tatsache. daß in etwa einem Drittel der Bluterfamilien ein ausgesprochener Kinderreichtum besteht, wird von *Schlößmann* ebenfalls durch Kompensation erklärt und findet im Tenner Bluterstamm durch die nachgewiesene Streuungsvergrößerung eine Bestätigung.

Mit dem Nachweis einer überdurchschnittlichen Fortpflanzungsrate eines Teils der Konduktorinnen ist aber noch nicht die Fortpflanzungseignung der Gesamtheit der Konduktorinnen bestimmt. Neben der bekannten Zahl der Blutermütter steht vorerst noch die unbekannte Zahl der übrigen Konduktorinnen, die Mütter sind, mit ihren Kindern. So wie die Blutermütter auch ohne die nachgewiesene Erhöhung der Kinderzahl schon eine Auslese nach hoher Kinderzahl darstellen, bilden die übrigen Konduktorinnen, die Mütter sind, entsprechend eine Auslese nach kleineren

Kinderzahlen, die bei deren Ermittlung berücksichtigt werden muß. — Als letztes muß dann noch die Zahl der kinderlosen Konduktorinnen ermittelt werden, um die gesuchte mittlere Zahl der Kinder pro Konduktorin endlich abschätzen zu können.

b. Die Zahl der übrigen Konduktorinnen, die Mütter sind, und die Zahl ihrer Kinder

Die Analyse der Kinderzahlen bei den Blutermüttern hat zur Hypothese geführt, daß ein Teil der Konduktorinnen nach dem Auftreten von Blutersöhnen noch eine vermehrte Zahl von nachfolgenden Kindern hat, die übrigen aber im normalen Rahmen bleiben. Unter dieser Hypothese ist es nun möglich, die vorerst unbekannte Zahl der übrigen Konduktorinnen, die Mütter sind, zu schätzen. Wir nehmen hier zunächst an, daß die Kinderzahl der Konduktorinnen die gleiche Verteilung hat wie in der Vergleichsbevölkerung. Daß dann sekundär einige Blutermütter noch zusätzliche Kinder haben, stört die Betrachtung nicht, weil die Nicht-Blutermütter hier interessieren.

Aus Tab. 5 geht hervor, daß, die abgeschnittene *Poisson*sche Verteilung vorausgesetzt, die verschiedenen Familiengrößen in folgenden Häufigkeiten vorkommen: (Tab. 10; a)

Durch Merkmalsträger, für welche angenommen wird, daß sie in jeder Familie mit der Wahrscheinlichkeit von $\frac{1}{4}$ auftreten können, werden aus jeder Familiengröße $1-\left(\frac{3}{4}\right)^z$ der Familien erfaßt. Nicht erfaßbar bleiben also $\left(\frac{3}{4}\right)^z$ (Tab. 10; b).

Von allen Konduktorinnen, die Mütter sind, haben also 40.9% keine Blutersöhne (Tab. 10; c). Dies unter der Voraussetzung, daß die Kinderzahlen dieser Mütter gleich verteilt sind wie in Teil A des Tenner Stammes.

Die 30 bekannten Blutermütter (Abb. 2) stellen also 59.1% aller Konduktorinnen, die Mütter sind, dar. Somit sind etwa 21 nicht durch Blutersöhne gekennzeichnete Mütter vorhanden, die aber doch Konduktorinnen sind. Nach Tab. 10; e, haben diese insgesamt 57 Kinder. Im Ganzen kann also mit 51 Konduktorinnen, die Mütter sind, gerechnet werden.

Ein ähnliches Resultat erhalten wir, wenn wir nur von der Zahl der Blutermütter, deren erstes Kind ein Bluter war, ausgehen. Diese Gruppe stellt ja $\frac{1}{4}$ aller Konduktorinnen, die Mütter sind, dar. Sie beträgt 12, was also auf 48 solche Konduktorinnen schließen läßt. Diese Schätzung ist aber mit einem relativ großen Fehler behaftet.

Tabelle 10

Berechnung der Anzahl Konduktorinnen, die Mütter sind, jedoch unter ihren Kindern keine Bluter haben und Berechnung der Anzahl ihrer Kinder

Calculation of the number of female carriers being mothers, but having no bleeders among their children and calculation of the number of their children

z	a	b	c	d	e
1	0,119	0,750	0,0893	4,55	4,55
2	0,201	0,563	0,1132	5,78	11,56
3	0,227	0,422	0,0958	4,88	14,64
4	0,192	0,316	0,0607	3,10	12,40
5	0,130	0,237	0,0308	1,57	7,85
6	0,073	0,178	0,0130	0,66	3,96
7	0,035	0,133	0,0047	0,24	1,64
8	0,016	0,100	0,0016	0,08	0,64
≥ 9	0,007	$\sim 0,05$	0,0003	0,01	$\sim 0,1$
Total	1,000	———	0,4094	20,87	57,3

z: Zahl der Kinder
  Number of children.
a: Zu erwartende Häufigkeit von Müttern mit z Kindern, bezogen auf alle Mütter (berechnet nach Tabelle 5, 3. Kolonne).
  Expected frequency of mothers with z children, related to all mothers (calculated according to table 5, column 3).
b: Anteil von Konduktorinnen mit z Kindern, von denen keines Bluter ist.
  $b = \left(\frac{3}{4}\right)^z$
  Proportion of female carriers with z children none of them being bleeder.
c: Häufigkeit von Konduktorinnen, die keine Bluter unter ihren Kindern haben.
  $c = a \cdot b$
  Frequency of female carriers who have no bleeders among their children.
d: wie c, auf 51 Konduktorinnen bezogen. (30 beobachtete Blutermütter = 59,1% aller Konduktorinnen mit Kindern.)
  $d = 51 \cdot c$
  like c, related to 51 female carriers. (30 observed mothers of bleeders = 59,1% of all female carriers which have children.)
e: Zahl der Kinder von d.
  $e = d \cdot c$
  Number of children of d.

c. Die Zahl der kinderlosen Konduktorinnen

Es bleibt nun noch die Frage nach der Zahl der kinderlosen Konduktorinnen. Zur Abschätzung dieser Größe nehmen wir an, daß in dieser Gruppe das Verhältnis der Kinderlosen zu den Müttern vom Blutergen unbeeinflußt ist. Aus Tab. 4 läßt sich die Häufigkeit der Mütter im Tenner Stamm wie folgt berechnen (Tab. 11):

Der Unterschied zwischen den beiden Teilen liegt im Bereich der Zufallsstreuung ($\chi^2 = 1,28$; $P = 26\%$). Deshalb benützen wir das Gesamtmaterial, um den Anteil der Mütter zu berechnen. Es sind 56%. Die 51 Konduktorinnen, die Mütter sind, bilden also 56% aller Konduktorinnen. Dies ergibt eine Gesamtzahl von 91 Konduktorinnen.

2

Tabelle 11

Der Anteil der Mütter unter den weiblichen Nachkommen des Tenner Stammes

Proportion of mothers among the female progeny of the Tenna kindred

	Mütter Mothers	Nichtmütter Non-mothers	Total
Teil / part A	82	57	139
Teile / parts B + C	57	53	110
Total	139 56%	110 44%	249

d. Die Fortpflanzungseignung der Konduktorinnen

Die Ergebnisse der vorigen Abschnitte sind in Tabelle 12 zusammengefaßt und liefern die durchschnittliche Kinderzahl aller Konduktorinnen und damit ihre Fortpflanzungseignung mit und ohne die frühesten Generationen.

Damit sind fünf Werte für g auf Grund dreier Berechnungsarten entstanden. Sie sind mit der Fortpflanzungseignung der Bluter in Tabelle 13 zusammengestellt.

Tabelle 13

Die Fortpflanzungsneigung der Bluter und der Konduktorinnen
im Bluterstamm von Tenna

The fitness of hemophiliacs and of female carriers in the kindred of Tenna

Bluter / bleeders			$f = 0{,}64$
Konduktorinnen / female carriers			
berechnet auf Grund von: calculated by:			
Vergleich zwischen Teil A und Teile B + C Comparison between parts A and B + C			$g_1 = 1{,}08$
Blutertöchter daughters of bleeders	alle all	Gener.	$g_2 = 1{,}32$
	nur only	Gener. IV–VIII	$g_3 = 1{,}61$
Blutermütter mothers of bleeders	alle all	Gener.	$g_4 = 1{,}17$
	ohne without	Gener. III–V	$g_5 = 1{,}14$

Tabelle 12

Die Fortpflanzungsneigung der Konduktorinnen

The fitness of female carriers

Konduktorinnen Female carriers			Zahl der Konduktorinnen Number of female carriers Generationen		Kinder Children Generationen	
			III-XI	VI-XI•	III-XI	VI-XI•
mit Kindern with children 56% (Tab. 11)	mit Blutersöhnen with bleeders among their children	59,1% (Tab. 10c)	30	27	162	138
	ohne Blutersöhne without bleeders among their children	40,9% (Tab. 10c)	21	19	57	52
ohne Kinder without children 44% (Tab. 11)			40	36	0	0
Total			91	82	219	190
Mittlere Kinderzahl Mean number of children					2,41	2,32
Teil / part A (Gen. V–Xa resp. VI–Xa)					2,06	2,03
Fortpflanzungseignung der Konduktorinnen Fitness of female carriers					$g_4 = 1{,}17$	$g_5 = 1{,}14$

Nur die Zahlen der ersten Zeile sind beobachtet, die übrigen sind berechnet.
Only the numbers in the 1st row are observed, the other numbers are calculated.

* Nur abgeschlossene Familien der XI. Generation.
• Only families of the XIth generation for which no further children may be expected.

Es zeigt sich also, daß im Bluterstamm von Tenna einer Fortpflanzungs-
einbuße bei den Blutern ein Fortpflanzungsvorteil bei den Konduktorinnen
gegenübersteht.

In bezug auf die Komponenten dieser Größe wäre noch zu untersuchen,
inwiefern für die vermutlichen Konduktorinnen die Verheiratungsziffer
beeinflußt wird. Da die Bevölkerung die Art des Erbganges seit langem
kennt, ist auch im allgemeinen bekannt, daß Töchter und Schwestern von
Blutern wieder Blutersöhne haben können. Dieser Einfluß des Familien-
milieus auf die Verheiratungsziffer der Töchter ist aus Tab. 14 (zusammen-
gestellt aus Tab. 11 der Monographie) zu entnehmen. Tatsächlich haben
sich von den Blutertöchtern und Bluterschwestern eine etwas geringere
Zahl verheiratet als von den übrigen Töchtern der Bluterlinien. Der Unter-
schied ist jedoch bei weitem nicht gesichert. Falls trotzdem in Wirklichkeit
ein gewisser Einfluß vorhanden wäre, ist allerdings der Anteil der Nicht-
Mütter in Tab. 11 und 12 eventuell etwas zu tief eingesetzt und die Fort-
pflanzungsneigungen g_4 und g_5 sind damit etwas zu groß angegeben worden.

D. Der Selektionswert des Blutergens

Wenn auch die verschiedenen Werte für die Fortpflanzungseignung der
Konduktorinnen zum Teil recht unsicher sind, so muß man doch für den

Tabelle 14

Einfluß des Familienmilieus auf die Verheiratungsziffer der Töchter (ohne Generation X b)
Frequency of marriages of daughters originating from hemophilic families

		ledig unmarried	verheiratet married	Total
mit Blutervater oder Bluterbrüder with hemophilic father or brothers	Teile / parts B + C	36 38,3%	58 61,7%	94
ohne Blutervater oder Bluterbrüder without hemophilic father or brothers	Teile / parts B + C	12 32,5%	25 67,5%	37
	Teil / part A	44 31,6%	95 68,4%	139

Keine gesicherten Differenzen
Differences not significant

Bluterstamm von Tenna mit einem Fortpflanzungsvorteil der Konduktorinnen rechnen. Damit nehmen Berechnungen der Mutationsrate, wie sie von *Haldane* und *Vogel* für die Gesamthämophilie durchgeführt wurden, für die hier vorliegende Form der Hämophilie B eine ganz andere Wendung. Es fragt sich nämlich, ob der Selektionsvorteil im weiblichen Geschlecht etwa schon genügen würde, um den Selektionsnachteil im männlichen Geschlecht zu kompensieren.

Unter welchen Bedingungen ein durch Selektion und Gegenselektion balanciertes System vorliegen könnte, sollen zum Schluß einige Berechnungen darlegen:

Wenn die Population im Gleichgewicht ist, bleibt die Häufigkeit der Bluter (x) und der Konduktorinnen (y) von Generation zu Generation unverändert. Die Bluter können ihr Gen nur von der Mutter haben, und zwar ist die Hälfte der Söhne von Konduktorinnen Bluter. Es ist also $x = \frac{1}{2}gy$. Umgekehrt sind alle Töchter von Blutern und die Hälfte der Töchter von Konduktorinnen wieder Konduktorinnen, also: $y = fx + \frac{1}{2}gy$. Diese beiden Gleichungen sind dann zugleich erfüllt, wenn $1 + f = \frac{2}{g}$, also $g = \frac{2}{1+f}$ ist. Unter diesen Bedingungen wird der Selektionsnachteil im männlichen Geschlecht durch den Selektionsvorteil im weiblichen Geschlecht gerade ausgeglichen.

Tab. 15 soll zeigen, daß dies für den Tenner Stamm durchaus im Bereich der gefundenen Werte liegt.

Im Gleichgewichtszustand ist das Verhältnis der Konduktorinnen zu

Tabelle 15

Fortpflanzungsnachteile bei den Blutern (f), die ohne Beteiligung von Mutationen durch die nebenstehenden Fortpflanzungsvorteile bei den Konduktorinnen (g) aufgehoben würden

The fitness of female carriers (g) which would balance the fitness of bleeders (f) without occurence of mutations

f	$g = \dfrac{2}{1+f}$
1,0	1,0
0,8	1,11
0,64	1,22
0,5	1,33
0,3	1,54
0	2,0

den Blutern $\frac{y}{x} = 1{,}64$. Es sind also 1,64mal mehr Konduktorinnen als Bluter zu erwarten. Nach Tab. 2 und 12 haben wir ein Verhältnis von $\frac{91}{53} = 1{,}72$ gefunden. Dieser Wert paßt also gut mit den Berechnungen der Fortpflanzungseignungen zusammen.

Falls sich die gefundenen Ergebnisse bei andern Stämmen der Hämophilie B bestätigen sollten, ist eine nach der bisher verwendeten Formel durchgeführte Bestimmung der Mutationsrate, wobei eine normale Fortpflanzungseignung der Konduktorinnen vorausgesetzt wird, illusorisch. Die Mutationsrate muß dann bedeutend geringer sein.

Zusammenfassung

Im Tenner Bluterstamm, der über 3 Jahrhunderte zurückreicht, ist der Fortpflanzungsnachteil der Bluter bisher relativ gering gewesen (f = 0,64). Der dadurch entstandene Verlust an Hämophiliegenen wurde durch eine erhöhte Kinderzahl der Konduktorinnen ausgeglichen (g ~ 1.2), und zwar besonders durch einen Teil der Blutermütter.

Summary

1. This investigation is based upon the extensive material presented in the paper of *Moor-Jankowski, J.K., Truog, G.T.* and *Huser, H.J.*: "Der Bluterstamm von Tenna und seine Nachkommen 1650–1955." Acta genet. 7, 1957. An attempt has been made to calculate the fitness of bleeders and of female carriers from the Tenna kindred of hemophilia (Type B).

2. In this kindred, no case of death by bleeding is recorded before the age of three years. The probability of the occurrence of the hemophilia gene is calculated for all boys who died at an early age. Thereby the number of the not yet manifest bleeders who died early is estimated.

3. The fitness of the bleeders is f = 0,64, i.e. considerably greater than the values from the calculations of *Haldane* (0.29) or of *Vogel* (0.39). (Tab. 2 and 3.)

4. The fitness of the female carriers (g) has been calculated in three different ways:

a) By comparing the females of the hemophilic families (Parts B and C of the Table of Descendants in *Moor-Jankowski* et al. 1957) with those of a branche without hemophiliacs (part A of the Table of Descendants in *Moor-Jankowski* et al. 1957), g > 1.08 (Tab. 4). The variance of the number of children from parts B and C significantly exeeds that from part A. Apparently, among the hemophilic families, there exists a group of mothers with exceptionally many children. (Abb. 1, Tab. 5, 6.)

b) The fitness of all daughters of bleeders is $g_2 = 1.32$ and for the earlier generations as much as 1.61. Here the variance is again greater than in part A. (Tab. 7, 8.)

c) Mothers of bleeders have significantly more children as one would expect by the special selection of the material. (Tab. 9.) Knowing the number of mothers of bleeders the remaining mothers who carry the hemophilia gene can be calculated. (Tab. 10.) These, added to the estimated number of female carriers without children (Tab. 11) provide an estimate of the total number of female carriers and of their children. The fitness is then $g \sim 1.15$. (Tab. 12.)

5. It has been shown that a fitness of bleeders of 0.64 can be balanced by a fitness of female carriers of 1.22 without the occurence of mutations. (Tab. 15.) The order of magnitude of the fitness values in the Tenna kindred leads to the conclusion that the selection in the bleeders could be countered by the increased number of children of the female carriers.

6. If similar results were obtained by further investigations on other kindreds with hemophilia B, this would mean that its rate of mutation is much less than the values so far reported.

Résumé

1. Les recherches sont basées sur le matériel très étendu qui se trouve dans le travail de *Moor-Jankowski, J.K., Truog, G. T.* et *Huser, H.J.*: «Der Bluterstamm von Tenna und seine Nachkommen». Acta genet. 7, 1957. Les auteurs ont essayé d'établir le degré de fécondité des hémophiles et des femmes conductrices dans la souche de Tenna, atteinte d'hémophilie (type B).

2. Dans cette souche, aucun décès dû à l'hémophilie n'est manifesté avant l'âge de 3 ans. La probabilité de la fréquence du gène de l'hémophilie se calcule pour tous les garçons morts en bas âge, ainsi on estime le nombre des hémophiles morts avant la manifestation de la maladie.

3. Le degré de fécondité des hémophiles est f = 0,64, c'est-à-dire beaucoup plus grand que les chiffres obtenus par *Haldane* (0.29) ou par *Vogel* (0.39). (Tableaux 2 et 3).

4. Le degré de fécondité des conductrices a été calculé de trois façons différentes:

a) En comparant les femmes des familles hémophiles (B, C) avec celles de la branche sans hémophilie (A), en ce qui concerne la descendance, $g > 1.08$ (Tab. 4). La variance du nombre des enfants dans les branches B et C dépasse significativement celle de la branche A. Apparemment il existe dans la branche hémophile de la famille un groupe de mères ayant énormément d'enfants. (Tab. 5, 6.)

b) Le degré de fécondité de toutes les filles de père hématophile est $g_2 = 1,32$ et va jusqu'à 1,61 pour les générations précédentes. Ici la variance est de nouveau plus grande que pour la branche A. (Tab. 7, 8.)

c) Les mères d'hémophiles ont significativement plus d'enfants que l'on prévoirait avec cette sélection spéciale du matériel. Connaissant le nombre des mères d'hémophiles, on peut calculer le reste des mères conductrices. (Tab. 10.) En tenant compte du nombre probable d'hétérozygotes sans enfants, on obtient une estimation du nombre total des conductrices et de leurs enfants. Le degré de fécondité est alors approximativement g = 1,15. (Tab. 12.)

5. Il a été possible de démontrer que le degré de fécondité des hémophiles qui, c.-à-d. 0,64, est balancé par le degré de fécondité des conductrices qui est de 1,22, sans qu'interviennent des mutations. (Tab. 15.) Le degré de fécondité relativement grand dans la souche de Tenna permet de conclure que l'effet de sélection chez les hémophiles est compensé par l'accroissement du nombre des enfants des femmes hétérozygotes.

6. Si des résultats semblables pouvaient être obtenus dans d'autres familles atteintes d'hémophilie B, ce serait alors la preuve que le taux de mutation est beaucoup plus petit qu'on le croyait jusqu'à présent.

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KLINISCHE, GENETISCHE UND GERINNUNGS-PHYSIOLOGISCHE ASPEKTE DER HÄMOPHILIE B BEI DEN BLUTERN VON TENNA, MIT EINEM BEITRAG ZUR GENETIK DER GERINNUNGSFAKTOREN

Von

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I. Einleitung

Die Kenntnis um die einzelnen Gerinnungsfaktoren ist noch jung und die Entwicklung der Gerinnungsphysiologie nicht abgeschlossen. Die Kenntnis um die Vererbung der einzelnen Gerinnungsfaktoren ist noch jünger. Die Bestandesaufnahme der Bluter aus dem Stamm von Tenna (MOOR-JANKOWSKI, TRUOG, HUSER, 1957) gab nun Anlaß zu genauen gerinnungsphysiologischen, klinischen und genetischen Untersuchungen, deren Resultate im folgenden dargestellt und anschließend besprochen sein sollen.

An Hand unserer Ergebnisse möchten wir dabei einen kurzen Überblick über die Ergebnisse der Gerinnungsphysiologie im allgemeinen und über die genetischen Aspekte der Gerinnungsphysiologie im speziellen geben. Dies ist der Inhalt der Kapitel I und II dieser Arbeit. In einem dritten und vierten Abschnitt werden sodann die Ergebnisse unserer Untersuchungen

über Farbensehen und Cyanidgeruchsempfinden bei den Nachkommen aus dem Bluterstamm von Tenna beschrieben.

Die Arbeit ist im Rahmen unserer Monographie «Der Bluterstamm von Tenna und seine Nachkommen 1650–1955», Acta genet. 7, 4., 1957, entstanden. Alle dort einleitend gebrachten Erörterungen gelten in vollem Umfang auch für die vorliegende Arbeit. Die verwendete Nomenklatur und die Bezeichnung der Probanden sind in beiden Arbeiten identisch.

Zu besonderem Dank verpflichtet sind wir auch hier den Herren Prof. A. Franceschetti, Privatdozent Dr. D. Klein, Prof. F. Koller und Prof. F. E. Lehmann für ihr reges Interesse, ihren Rat und ihre Unterstützung.

Der Schweizerische Nationalfonds zur Förderung der wissenschaftlichen Forschung hat die Bestandesaufnahme in den Jahren 1955 und 1956 unterstützt und die gerinnungsphysiologischen Analysen ermöglicht.

Das Krankheitsbild der Hämophilie beruht auf einer hämorrhagischen Diathese, d. h. auf einer abnorm gesteigerten Blutungstendenz und ist charakterisiert durch eine spezifische klinische Syndromatik. Diese ist gekennzeichnet durch die meist schon in der frühen Jugend einsetzenden, langanhaltenden und kaum stillbaren Blutungen, welche bereits nach geringfügigen Verletzungen auftreten, im weiteren durch massive Spontanblutungen in Haut, Schleimhäute und Gelenke sowie durch oft erst nach Tagen eintretende Nachblutungen

Dieses klassische Krankheitsbild weist einen typischen, rezessiv geschlechtsgebundenen Erbgang auf.

Bis vor kurzem wurde so die Bluterkrankheit als *nosologische Einheit* mit typischem Erbgang und charakteristischem Krankheitsbild aufgefaßt, wobei man über das eigentliche Wesen der Krankheit lediglich annehmen konnte, daß es sich wahrscheinlich um eine X-chromosomal vererbte Verzögerung der Blutgerinnung handeln mußte, zumal bei praktisch allen Hämophilen die Blutgerinnungszeit abnorm lang war und das Blut oft viele Stunden ungeronnen blieb.

Das Wesen der Blutgerinnung beruht letztlich auf der Umwandlung von Fibrinogen in Fibrin. Diese Umwandlung ist die Endreaktion einer Reihe von biologisch-chemischen Prozessen, deren Ablauf Morawitz (1905) zu folgendem Schema zusammengefaßt hat:
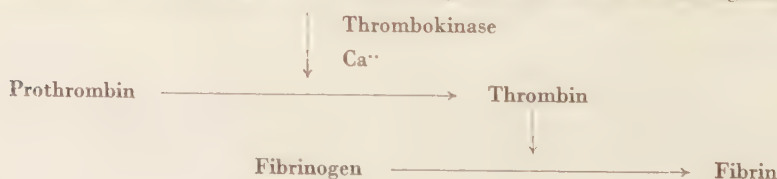
Abb. 1

Erst die in den jüngsten Jahren erfolgte Entwicklung der gerinnungsphysiologischen Untersuchungsmethoden brachte hier weitere Klärung, indem nun die verschiedenen Phasen der Gerinnung getrennt untersucht und analysiert werden konnten:

1947 fügte OWREN den vier bekannten Gerinnungsfaktoren Fibrinogen (I), Prothrombin (II), Thromboplastin (III) und Ca·· (IV) den Faktor V bei, welcher seinerseits in seiner aktivierten Form als Faktor VI bezeichnet wird. Später sind noch weitere Faktoren entdeckt worden. Da diese Faktoren oft von verschiedenen Forschungsgruppen unabhängig entdeckt und untersucht worden sind, bestehen für ihre Bezeichnung nach wie vor eine Anzahl Synonyma. Einen Überblick über die gebräuchlichsten Bezeichnungen gibt Tabelle I. Wir halten uns im weiteren an die an der I. Internationalen Tagung über Thrombose und Embolie 1954 von einem internationalen Komitee festgelegte Nomenklatur, welche in Kolonne 1 der Tabelle I angeführt ist.

Unter Berücksichtigung dieser Erkenntnisse läßt sich das Gerinnungsschema von MORAWITZ zwanglos erweitern und wie folgt zusammenfassen:

Hagemann-Faktor — PTA-Faktor — Faktor VIII + Faktor IX + Stuart-Prower-Faktor
+ Faktor X + Faktor V + Plättchenfaktor + Ca··

$$\vee$$

Blutthromboplastin

$$\downarrow$$

Prothrombin $\longrightarrow$ Thrombin

$$\downarrow$$

Fibrinogen $\longrightarrow$ Fibrin
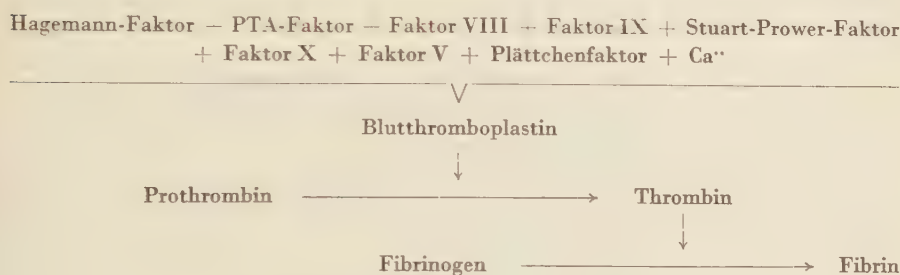
Abb. 2

Das Fehlen *eines* dieser Gerinnungsfaktoren bedingt eine hämorrhagische Diathese, da es zu einer vollständigen Blutgerinnung sämtlicher Faktoren bedarf.

Dabei kann das Fehlen der *Gerinnungsfaktoren vererbt* oder *erworben* sein.

Einen Überblick über die einzelnen Möglichkeiten gibt Tabelle II.

Die vorliegende Arbeit befaßt sich im weiteren lediglich mit dem vererblichen Mangel der Gerinnungsfaktoren im allgemeinen und mit dem erblichen Mangel an Faktor IX im speziellen. Ein *erblicher* Mangel unterscheidet sich von den erworbenen Formen vor allem durch das *isolierte* Fehlen *eines* Gerinnungsfaktors, während bei hämorrhagischen Diathesen auf *erworbener* Grundlage fast immer *mehrere Gerinnungsfaktoren gleichzeitig* in ungenügendem Maße vorhanden sind.

Was nun die *klassische Hämophilie* anbetrifft, so kann sie heute *nicht* mehr als nosologische Einheit betrachtet werden, haben doch die gerinnungsphysiologischen Untersuchungen ergeben, daß dasselbe klinische Krankheitsbild mit demselben genetischen Erbgang auf dem *Fehlen zweier qualitativ verschiedener Gerinnungsfaktoren* beruhen kann, nämlich auf dem Fehlen der Faktoren VIII oder IX (ADDIS, 1911, LEWIS, TAGHON, DAVIDSON, MINOT und TAYLOR, 1946, KOLLER, KRÜSI und LUCHSINGER, 1950, BIGGS, DOUGLAS, MACFARLANE, DACIE, PITNEY, O'BRIEN, 1952).

Tab. I. Synonyma der Gerinnungsfaktoren

Name	Nr.	Synonyma
Fibrinogen	I	Fibrinogen (DENIS)
Prothrombin	II	Prothrombin (SCHMIDT) Thrombogen (MORAWITZ) Thrombozym (NOLF) Serozym (BORDET) Plasmozym (FULD)
Thromboplastin	III	Thromboplastin (NOLF) Thrombokinase (MORAWITZ) Zymoplastin (SCHMIDT) Cytocym (BORDET) Thrombokinin (LENGGENHAGER)
Kalzium	IV	
Faktor V	V	Faktor V (OWREN) Proaccelerin (OWREN) labile factor (QUICK) Prothrombin Accelerator (FANTL und NANCE) Plasma accelerator-globulin (WARE und SEEGERS) Thrombogene (NOLF) Prothrombokinase (MILSTONE) Plasma-prothrombin-conversion-factor (STEFANINI)
Faktor VI	VI	Faktor VI (OWREN) Accelerin (OWREN) Serum-Accelerator-Globulin (WARE und SEEGERS) Serum Accelerator (STEFANINI)
Faktor VII	VII	Faktor VII (KOLLER) Proconvertin (OWREN) Stable factor (STEFANINI) Co-factor (OWREN) Serozym (BORDET) Co-Thromboplastin (MANN und HURN)
Faktor VIII	VIII	Faktor VIII (KOLLER) Antihämophiles Globulin (PATEK und TAYLOR) Antihämophiles Globulin A (CRAMER) Antihemophilie factor (BRINKHOUS u. a.) Plasma thrombo plastic factor (PTF) (RATNOFF) Plasma thromboplastic factor A (AGGELER) Facteur antihémophilic A (SOULIER) Thrombokatalysin (LENGGENHAGER)
Faktor IX	IX	Faktor IX (KOLLER) Christmas factor (BIGGS und MACFARLANE) Plasma-thromboplastic Component (PTC) (AGGELER) Antihämophiles Globulin B (CRAMER)
Stuart-Prower-Factor		Stuart-Faktor (HOUGIE, BARROW, GRAHAM) Stuart-Prower-Faktor (BACHMANN, DUCKERT, GEIGER, BAER)
Hagemann-Faktor		Hagemann-Faktor (MARGOLIUS und RATNOFF)

Anmerkung: Nur die gebräuchlichsten Bezeichnungen wurden erwähnt, für vollständige Angaben und Literaturverzeichnis siehe DEUTSCH 1955.

Nach KOLLER (1953) sprechen wir bei einem Mangel an Faktor VIII von *Hämophilie A*, bei einem Mangel an Faktor IX von *Hämophilie B*. Beide Formen werden rezessiv geschlechtsgebunden vererbt.

Andererseits haben die Untersuchungen von NILSSON, BLOMBÄCK und FRANCKEN (1957) gezeigt, daß es auch eine autosomal vererbte Form eines Faktor VIII-Mangels gibt, indem sie bei 6 Mädchen und 3 Knaben aus 6 verschiedenen Familien eine hämorrhagische Diathese bei einem Faktor VIII-Mangel von 1–10% der Norm beschrieben haben. Falls sich diese Angaben an noch größerem Material bestätigen lassen, scheint die Tatsache vorzuliegen, daß sich einerseits verschiedene Gerinnungsfaktoren genetisch gleich verhalten (z. B. Faktor VIII und Faktor IX) und andererseits der Mangel an ein und demselben Faktor verschiedene Vererbungsgänge aufweisen kann (X-chromosomaler und autosomaler Faktor VIII-Mangel).

In diesem Zusammenhang sei auch kurz die vaskuläre Hämophilie A und B erwähnt, welche erstmals von SHULMAN, SMITH, ERLANDSON, FORT und LEE (1956) und von MATTER, NEWCOMB, MELLY und FINCH (1956) beschrieben worden sind. Wenn auch diese Krankheitsbilder in ihren Einzelheiten noch nicht völlig geklärt sind, so sind sie doch von großem theoretischem Interesse. Es handelt sich dabei um hämorrhagische Diathesen mit hämophilieähnlichem Blutungstyp, welche auf einem kongenitalen partiellen Mangel an Faktor VIII bzw. an Faktor IX beruhen und kombiniert sind mit einer nicht genauer umschreibbaren vaskulären Störung. Die vaskuläre Störung zeigt sich in einer verlängerten Blutungszeit nach DUKE und in einer erhöhten Kapillarbrüchigkeit.

Die Thrombozytenzahl ist normal, beide Geschlechter werden betroffen, und die Vererbung erfolgt nach ACHENBACH (1957) dominant. Auf diese Kombination, bestehend aus einem Gerinnungsdefekt mit einer begleitenden, nicht genauer umschreibbaren, vaskulären Störung, soll an Hand unserer eigenen Ergebnisse noch eingetreten werden.

Die Vererbung der *übrigen* Gerinnungsfaktoren scheint rein *autosomal* zu erfolgen. Die heute von den verschiedenen Autoren angenommenen Erbgänge sind auf Tab. II zusammengestellt und mit den entsprechenden Literaturangaben belegt worden.

Dazu möchten wir vorausschicken, daß in der Bibliographie nur größere, genetisch verwertbare Arbeiten vermerkt worden sind. Ein ausführliches Literaturverzeichnis über die Faktoren V und VII sowie über den Stuart-Prower-Faktor wird zurzeit von BACHMANN (1958) zusammengestellt. Einigermaßen sichergestellt ist der Erbgang indessen erst für die Faktoren V, VII, VIII, IX und den Stuart-Prower-Faktor.

Der von KOLLER (1953) postulierte Faktor X scheint in seinem Effekt weitgehend auf dem von TELFER, DENSON und WRIGHT (1956), HOUGIE, BARROW und GRAHAM (1957)

Tab. II. Die Gerinnungsfaktoren, ihr Mangel und ihre Vererbung

Gerinnungsfaktor	Erworbener Mangel	Hereditär konstitutioneller Mangel	Erbgang	Literatur
Fibrinogen	Leberaffektionen, Knochenmarksaffektionen	Afibrinogenämie, Fibrinopenie	rezessiv (?)	CAUSSADE, NEIMANN, PIERSON, MANCIAUX 1954; FRICK 1954; VANDENBROUCKE, VERSTRAETE, VERWILGHEN 1954
Prothrombin	Leberaffektionen, Mangel an Vitamin K, Cumarinüberdosierung Neugeborene	Idiopathische Hypoprothrombinämie	autosomal rezessiv (?)	QUICK 1955
Thromboplastin	siehe Faktoren VIII bis Hagemann			
Calciumionen	Eine Verminderung des Blutcalciums führt zum Tode, bevor eine Gerinnungsverzögerung eintritt			
Faktor V und VI	Leberaffektionen	Parahämophilie (Morbus Owren)	dominant mit unvollständiger Penetranz	KINGSLEY 1954; LARRIEU, CAEN, GRENET, CAYLA, BERNARD 1956
Faktor VII	Leberaffektionen, Mangel an Vitamin K, Cumarinüberdosierung Neugeborene	Kongenitaler Faktor VII-Mangel	autosomal intermediär	OWREN 1953; ZOLLINGER 1958
Faktor VIII	Hemmkörperhämophilie, vorzeitige Plazentalösung	Hämophilie A / Angiohämophilie A Kongenitaler Faktor VIII-Mangel	rezessiv geschlechtsgebunden dominant / dominant mit wechselnder Expressivität	VOGEL 1955 / ACHENBACH 1957 NILSSON, BLOMBÄCK, von FRANCKEN 1957
Faktor IX	Leberaffektionen, Mangel an Vitamin K, Cumarinüberdosierung	Hämophilie B / Angiohämophilie B	rezessiv geschlechtsgebunden dominant	VOGEL 1955; MOOR-JANKOWSKI, TRUOG, HUSER 1957 ACHENBACH 1957
Stuart-Prower-Faktor (Faktor X?)	Leberaffektionen, Mangel an Vitamin K,	Konstitutioneller Stuart-Prower-Faktor-Mangel	autosomal unvollständig, rezessiv mit starker Penetranz / autosomal-intermediär	GRAHAM, BARROW, HOUGIE 1957 BACHMANN 1958
PTA		Kongenitaler PTA-Mangel	autosomal dominant (?)	ROSENTHAL 1954
Hagemann-Faktor		Kongenitaler Faktor-Hagemann-Mangel	autosomal rezessiv (?)	MARGOLIUS und RATNOFF 1956

sowie BACHMANN, DUCKERT und FLÜCKIGER (1957) beschriebenen Stuart-Prower-Faktor zu beruhen (DUCKERT, 1957).

Für den *familiären Faktor V-Mangel* hat KINGSLEY (1954) zwei Familien beschrieben, in welchen quantitative Faktor V-Bestimmungen durchgeführt worden sind.

Dabei zeigt sich in Familie 2 (Mz nach KINGSLEY) folgende Konstellation:

Mz 1	Faktor V-Aktivität	29%	klinische Manifestation	: 0
Mz 2		30%		: 0
Mz 3		103%		: 0
Mz 4		0%		: +
Mz 5		0%		: +
Mz 6		42%		: 0
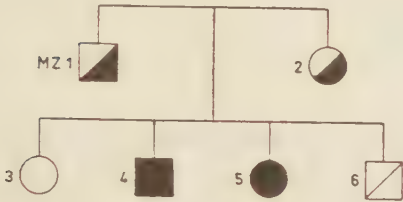
Abb. 3.

Familiärer Faktor V-Mangel
(nach Kingsley 1954)

Da jedoch bei vermutlich Heterozygoten der Familie 1 wechselnde Faktor V-Aktivitäten von 24–68% *und* wechselnde klinische Manifestationen vorkommen, schreibt KINGSLEY zusammenfassend: «... The hereditary mechanism of familial Factor V deficiency is shown to be transmitted by a gene, which although clinically recessive in these families, nevertheless has a potency roughly equal to its counterpart. In addition it is shown, that the gene displays a degree of variable expressivity and it is suggested, that cases may be encountered, in which the gene is either completely recessive or partially dominant.»

ZOLLINGER (1958) beschreibt den bisher größten Stammbaum eines *familiären Faktor VII-Mangels* und findet dabei genetisch analoge Verhältnisse. Der Erbgang wird dabei als *autosomal intermediär* bezeichnet. Ein intermediärer Erbgang ist dadurch charakterisiert, daß das betreffende Erbmerkmal sich in seiner Manifestation bald wie rezessiv und bald wie dominant verhält.

Die Vererbung des *Stuart-Prower-Faktors* erfolgt nach BACHMANN, DUCKERT, GEIGER, BAER und KOLLER (1957) nach gleichen Prinzipien: vermutlich heterozygote Probanden zeigen, ohne klinisch manifest zu sein, einen Gehalt an *Stuart-Prower*-Faktor von 25 bis 60% und der klinisch

schwer manifeste Proband zeigt 0%, so daß BACHMANN (1958) auf Grund einer Familienanalyse von ca. 60 Probanden auch hier einen *autosomal intermediären* Vererbungstyp postuliert.

Bei diesen autosomal vererbten Koagulopathien lassen sich demnach heterozygote Probanden gerinnungsphysiologisch feststellen, ja unter Umständen sind sie sogar klinisch manifest. Jedenfalls sind die Ergebnisse in dieser Richtung viel eindeutiger und ganz anders als bei den heterozygoten Konduktorinnen der rezessiv geschlechtsgebundenen Hämophilie. Wir werden im nächsten Abschnitt noch darauf zurückkommen.

Und wenn wir einleitend festgestellt haben, daß die «Hämophilie» nicht mehr als nosologische Einheit aufgefaßt werden kann, indem zahlreiche Faktoren neu mitberücksichtigt werden müssen, so möchten wir nach all dem Gesagten doch an dem Begriff der *klassischen Hämophilie festhalten und darunter all diejenigen Koagulopathien verstehen, welche durch den Mangel irgend eines Gerinnungsfaktors bedingt sind und einen rezessiv geschlechtsgebundenen Erbgang aufweisen.*

II. Hämophilie B, ein rezessiv-geschlechtsgebundener Faktor IX-Mangel

Im Verlaufe unserer Bestandesaufnahme konnten 67 Probanden aus dem Bluterstamm von Tenna einer gerinnungsphysiologischen Untersuchung zugeführt werden. Davon sind

> 10 Bluter,
> 4 Bluterbrüder,
> 11 sichere Konduktorinnen,
> 32 mögliche Konduktorinnen,
> 8 Söhne möglicher Konduktorinnen,
> 2 Söhne von Blutern.

Der bei jedem Probanden aufgenommene Gerinnungsstatus umfaßt die Bestimmung von: Prothrombinzeit nach Quick, Fibrinogen, Faktor V, Faktor VII, Prothrombin-Consumption, Faktor IX.

a) *Methodik*

Mit Ausnahme der Quickschen Prothrombinzeit wurden die laboreigenen Methoden des Gerinnungslabors (Prof. F. KOLLER) der Medizinischen Universitätsklinik Zürich (Dir. Prof. RÖSSLER) durchgeführt. Gerinnungsphysiologisch äußern sich die Hämophilien in einem quantitativen Mangel an Faktor VIII oder Faktor IX, einer ungenügenden Thromboplastinbildung, einer verminderten Prothrombinconsumption und in einer Verlängerung der Rekalzifizierungszeit. Zur Bestimmung von Faktor VIII wurde eine Modi-

fikation der Methode von K. M. BRINKHOUS (1954) verwendet. Die Bestimmung von Faktor IX erfolgte nach der von GEIGER (1956) eigens entwickelten Einstufen-Methode deren Prinzip darauf beruht, daß zu einem Substrat, welches alle Gerinnungsfaktoren außer dem zu testenden im Überschuß enthält, das Probandenserum zugegeben wird, worauf man nach Rekalzifizierung die Gerinnungszeit bestimmt.

Es wurde also zu einem Hämophilie-B-Plasma mit einem Faktor IX-Gehalt von 0°₀ Probandenserum mit unbestimmtem Faktor IX-Gehalt beigegeben und hierauf nach Rekalzifizierung die Gerinnungszeit bestimmt. Um möglichst vergleichbare Seren zu erhalten, werden die Seren aus zentrifugiertem Oxalatplasma hergestellt, das nach Verdünnung mit Veronal-Acetat-Puffer und Zugabe von verdünnter Hirnthrombokinase rekalzifiziert und 3 Stunden bei 37° inkubiert wird.

0,2 ccm Oxalatplasma
1,4 ccm Veronal-Acetat-Puffer
0,2 ccm Hirnthrombokinase, 1:10 verdünnt
0,2 ccm CaCl₂-Lösung m/40

Nach der Inkubation werden die Seren zur Elimination der nicht inaktivierten Hirnthrombokinase 30 Minuten bei 26 000 g und 4°C zentrifugiert.

Alle Reagenzien werden im Deep freezer aufbewahrt. Vor der Bestimmung werden sie eine Stunde in gewöhnlichen Glasröhrchen bei Zimmertemperatur stehen gelassen.

Zur Bestimmung werden gemischt:

0,1 ccm Hämophilie B-Oxalat-Plasma (Substrat ohne Faktor IX)
0,1 ccm Kontroll- oder Probandenserum (bei der Herstellung schon 1:10 verdünnt)
0,1 ccm Chloroformextrakt aus Hirnthrombokinasepulver 1:100 verdünnt (partielles Thromboplastin).

Nach 30 sec. Inkubation bei 37°C wird rekalzifiziert:

0,1 ccm CaCl₂-Lösung m/40

Die Gerinnungszeit wird unter dauerndem Kippen des 1×10 ccm messenden Glasröhrchens in der Inkubationswanne bei 37° C bestimmt. Hierauf wird der Faktor IX-Gehalt auf einer Eichkurve abgelesen. (Eichkurve Abb. 4.)

Wie Kontrolluntersuchungen ergeben haben, ist diese Methode mit einem Fehler von $\pm 100\%$ behaftet, d. h., ein mit 4% bestimmter Faktor IX-Gehalt ist als Wert innerhalb von 2% bis 8% aufzufassen. Trotz dieser großen Streubreite ist die beschriebene Einstufenmethode bis heute wohl das quantitativ genaueste Verfahren zur Bestimmung des Faktor IX-Gehaltes.

Die Endergebnisse dieser Untersuchung sind auf Tabelle 3 zusammengestellt. Bluter und Konduktorinnen werden dabei einzeln aufgeführt, während von den gesunden Probanden nur die gefundenen Extremwerte angegeben werden.

Speziell wird ferner die mögliche Konduktorin C. X. 629 angeführt, da sie eine im Doppelversuch gesicherte pathologische Prothrombinconsumption aufweist.

b) *Resultate und Besprechung*

1. Die Bluter

Alle untersuchten Bluter zeigen einen Faktor IX-Mangel von 2,5–6%
der Norm, was *gerinnungsphysiologisch einer mittelschweren Hämophilie B*
entspricht. Bei schweren Hämophiliewerten finden sich in der Regel Werte
von unter 1% der Norm.

Die Faktor VIII-Werte sind bei allen Probanden im Bereich der Norm,
eine Hämophilie A kann demnach mit Sicherheit ausgeschlossen werden.
Neben dem eindeutigen Mangel an Faktor IX läßt sich bei allen Blutern eine
Verlängerung der Rekalzifizierungszeit und eine Verschlechterung der
Prothrombin-Consumption feststellen, was, wie wir bereits dargelegt haben,
für Hämophilieblut charakteristisch ist.

Auffallend ist, daß bei den 10 untersuchten Blutern die Faktor IX-
Werte in einem sehr engen Bereich liegen, ja praktisch identisch sind. Dabei
ist zu berücksichtigen, daß, wie aus unserer Abb. 5 hervorgeht, sich die
einzelnen manifesten Probanden wohl über 13 Generationen auf gemein-
same Vorfahren zurückführen lassen, daß sie aber bei dem weitverbreiteten
Bluterstamm im einzelnen mehr als untereinander verwandt bezeichnet
werden können und somit, abgesehen von dem X-chromosomal vererbten
Hämophiliegen in ihren übrigen Erbanlagen ziemlich heterogen sein dürf-
ten. Der Manifestationsgrad des Hämophiliegens ist jedoch quantitativ
gesehen bei allen Blutern praktisch derselbe, nämlich 2.5–6% der Norm,
was zur Annahme berechtigt, daß es sich bei der Hämophilie B des Bluter-
stammes von Tenna um eine *familiäre Mutante des Hämophilie B-Gens*
handelt. Anders formuliert würde dies bedeuten, daß sich das Hämophilie
B-Gen im Blut mehr oder weniger direkt im Faktor IX-Mangel manifestiert.

Diese Annahme ist bereits durch das im Laboratorium von KOLLER
festgestellte Vorliegen völlig analoger Verhältnisse bei Hämophilie A-
Sippen erhärtet worden, indem in ein und derselben Sippe nie schwere und
leichte Hämophilie-Fälle nebeneinander vorkommen. Dies wiederum be-
deutet, daß der Genetik in der quantitativen Bestimmung des Mangels
eines Gerinnungsfaktors eine Methode zur Verfügung steht, welche erlaubt,
den Manifestationsgrad eines Genes in bezug auf diesen Gerinnungsfaktor
mehr oder weniger direkt zu bestimmen. Daraus, sowie aus dem entspre-
chenden klinischen Erscheinungsbild andererseits, würde sich sodann die
Bedeutung modifizierender Faktoren auf den klinischen Phänotypus eini-
germaßen ableiten lassen.

Wenn wir nämlich an unserem Material die *klinische Manifestation der*
Hämophilie berücksichtigen, wie sie im speziellen Teil unserer Arbeit

EINSTUFIGE FAKTOR IX – BESTIMMUNG BEI DEN BLUTERN UND KONDUKTORINNEN VON TENNA   (Faktor IX = Christmas Factor = PTC)
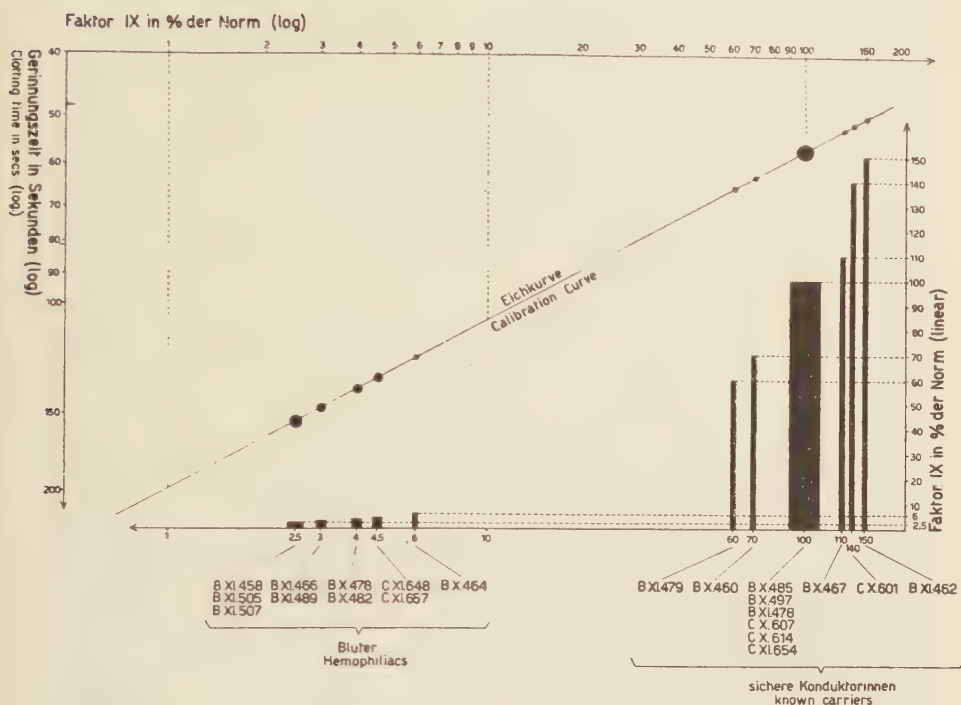
ONE-STAGE DETERMINATION FACTOR IX IN THE SERUM OF THE HEMOPHILIACS
AND CARRIERS OF TENNA

Abb. 4.

(MOOR-JANKOWSKI, TRUOG, HUSER) eingehend beschrieben und in der Diskussion auf Seite 81 ff. besprochen wurde, so kommen wir zu folgendem Ergebnis:

Allgemein klinisch gesehen handelt es sich um eine *mittelschwere Hämophilie*, d.h.,

1. es besteht die Tendenz zu multiplen Blutungserscheinungen wie Nasenbluten, Gelenksblutungen, Blutungen in die Weichteile usw.;

2. gelegentlich kommen Spontanblutungen vor;

3. bedingen die Blutungen in ihrem Ausmaß keine größeren bleibenden Schäden, so daß alle Erkrankten einen Beruf ausüben können.

Innerhalb dieses Rahmens der klinisch mittelschweren Hämophilie bestehen nun aber große *individuelle Unterschiede*. Diese Unterschiede betreffen sowohl das Manifestationsalter, wie auch den Manifestationsgrad

der Erkrankung und die jeweils vorherrschende Blutungstendenz. Neben Fällen mit fast gleichmäßigem Auftreten aller Blutungsarten, wie z. B. bei B X.464 oder C XI.644 kommen auch Erscheinungsbilder vor, in welchen die eine oder andere sonst charakteristische hämophile Blutungsart vollständig fehlt. So fehlt Nasenbluten bei C X.630 und B XI.505, Blutungen aus dem Mund und Suffusionen fehlen bei C XI.657. In andern Fällen wird das Bild durch eine hämophile Blutungsart vollständig dominiert, so durch Muskelblutungen bei B X.462 oder durch Gelenksblutungen bei B XI.466. Als besonderes Beispiel individueller Unterschiede sei hier nochmals auf die zwei unter gleichen Bedingungen aufgewachsenen Brüder (B XI.505 und B XI.507) hingewiesen, wovon einer, B XI.505, seit dem ersten Lebensjahr an multiplen Blutungserscheinungen leidet, wogegen der andere, B XI.507, bis zu seinem heutigen *fünften Lebensjahr* überhaupt *keine* klinisch feststellbare Blutungsbereitschaft zeigt. Wie aus Tabelle II ersichtlich ist, weisen nun aber beide Brüder den genau gleichen Faktor IX-Gehalt von 2,5% der Norm auf. Weitere individuelle Unterschiede zeigen sich bei dem Abklingen der Blutungserscheinungen mit dem Alter. So sind z. B. bei C XI.648, der in früher Jugend unter fast allen Blutungsarten stark gelitten hat, seit dem 30. Lebensjahr praktisch überhaupt keine *Blutungen mehr* aufgetreten, während B X.464 heute mit 53 Jahren nur eine teilweise Abnahme der Blutungsbereitschaft zeigt. Dabei betragen die entsprechenden Faktor IX-Werte 4,5% für C XI.648 bzw. 9% für B X.464.

Individuelle Unterschiede lassen sich schließlich auch in der Manifestation der hämophilen Nachblutung feststellen, welche bei den einzelnen Probanden in sehr verschiedenem Maße auftritt.

Zusammenfassend können wir sagen, daß sich das Hämophilie B-Gen im Bluterstamm von Tenna gerinnungsphysiologisch mehr oder weniger direkt als Faktor IX-Mangel manifestiert, daß aber bei der klinischen Manifestation modifizierende Faktoren konstitutioneller Art eine Rolle spielen. Im Bluterstamm von Tenna ist demnach bei einzelnen *Probanden die Hämophilie klinisch nicht manifest* und läßt sich nur gerinnungsphysiologisch diagnostizieren.

Die Hämophilie gehört zu den Koagulopathien, d. h. zu denjenigen hämorrhagischen Diathesen, welche durch Gerinnungsstörungen verursacht werden. Koagulopathien beruhen im wesentlichen auf Störungen in den biologisch-chemisch ablaufenden Gerinnungsmechanismen. Ihnen lassen sich die eher *mechanisch* bedingten Diathesen gegenüberstellen, bei welchen die Abdichtung des Blutstromes gegen das Gewebe durch die Gefäßwände oder durch Thrombocytenagglutinationen ungenügend ist.

Innerhalb der Koagulopathien beruht die hämophile Gerinnungsstörung, wie aus dem Gerinnungsschema ersichtlich ist, auf einer verminderten *Thromboplastinbildung.* (Abb. 2)

Wie aus dem Zahlenmaterial von Tab. III hervorgeht, verläuft auch die weitere Blutgerinnung bei den Tenner Blutern weitgehend parallel, so

Tab. III. Gerinnungsphysiologische Bestandesaufnahme der Nachkommen aus dem Bluterstamm von Tenna

Standortnummer	Quick' Prothr.zeit %	Faktor I mg%	Faktor II %	Faktor V %	Faktor VII %	Faktor VIII %	Rekalz.-zeit sec.	Prothr. Cons. %	Faktor IX %
Im Labor gefundene Normalwerte	70–100	200–500	70–100	50–100	70–100	60–180	60–150	1–3	60–180
Bluter									
B XI. 458	100	350	80	100	100		--	–	2,5
B X. 464	85	250	100	75	100	130	220	13	6
B XI. 466	85	350	80	90	80	110	190	15	3
B X. 478	85	350	90	70	90	130	210	13	4
B X. 482	70	350	90	65	85	90	270	5	4
B XI. 489	75	250	90	75	85	70	200	8	3
B XI. 505	100	300	100	100	100	140	220	11	2,5
B XI. 507	100	350	100	90	100	110	250	23	2,5
C XI. 648	100	300	100	100	100	150	230	30	4,5
C XI. 657	90	300	100	95	100	120	240	6	4,5
Konduktorinnen									
B X. 460	100	300	100	90	100	90	120	3	70
B XI. 462	85	300	90	75	90	120	130	1,5	150
B X. 467	75	350	90	80	85	100	110	1,5	110
B XI. 478	100	300	100	100	100	120	110	1	100
B XI. 479	75	250	90	60	85	100	120	1	60
B X. 485	90	275	100	80	100	70	110	1	100
B X. 497	85	350	100	85	100	110	150	1,5	100
C X. 601	100	350	100	100	100	130	120	1,5	140
C X. 607	85	350	90	90	90	120	130	1,5	100
C X. 614	100	300	100	90	90	90	95	1	100
C XI. 654	80	200	90	100	90	150	125	2	100
Mögliche Konduktorin									
C X. 629	100	300	100	65	95	100	100	23	100
Übrige Tenner (45) (Extremwerte)	80–100	200–500	80–100	60–100	80–100	60–160	80–145	1–2	65–150

daß sich aus dem Gerinnungsablauf allein mindestens mit den uns heute zur Verfügung stehenden Untersuchungsmethoden keine Anhaltspunkte für die Divergenzen im klinischen Bild ergeben.

Dabei sind nun allerdings die eher mechanischen Komponenten der Blutstillung nicht berücksichtigt worden, also die Abdichtung der Gefäße durch Vasokonstriktion und die Agglutination der Thrombozyten. Bei Störungen dieser Art ist charakteristischerweise die Blutungszeit stark verlängert und die Gerinnungszeit normal, während bei den biologisch chemisch bedingten Koagulopathien die Gerinnungszeit stark verlängert und die Blutungszeit normal ist.

Die *Blutungszeit* ist in erster Linie ein Maß für die Reaktion der Kapillaren, weil der Hauptfaktor, der die Blutung aus kleinen Hautwunden kontrolliert, in der Konstriktion der lädierten kleinen Blutgefäße zu sehen ist. Die Bestimmung erfolgt nach Duke (1910) durch einen 3–4 mm tiefen Stich in das Ohrläppchen oder eine Fingerbeere, wobei das austretende Blut alle 15–30 Sekunden abgetupft wird.

Demgegenüber gibt die Gerinnungszeit ein Maß für den Ablauf des eigentlichen Gerinnungsprozesses (siehe Abb. 2). Die Methodik der Bestimmung erfolgt meist nach Lee und White (1913).

Wie nun weiterhin aus den Krankengeschichten und den gerinnungsphysiologischen Untersuchungsergebnissen bei den Blutern aus dem Stamm von Tenna hervorgeht, weisen die meisten bei laboratoriumsmäßig gleichen Befunden sehr unterschiedliche klinische Manifestationen auf. Die klinische Manifestation besteht, wie bereits erörtert wurde, in Blutungen in das Gewebe oder in Körperhöhlen. Einer schweren klinischen Manifestation entspricht logischerweise eine länger dauernde Blutung, so daß der Schluß naheliegt, die Unterschiede in der klinischen Manifestation könnten letztlich durch Unterschiede in der Blutungs*dauer* bedingt sein. Die Veränderung der Blutungs*zeit* mag dabei nur sehr geringfügig und laboratoriumsmäßig nicht feststellbar sein. Die individuellen Unterschiede der hämophilen Manifestation im Stamm der Bluter von Tenna könnten somit am ehesten durch *konstitutionelle Gefäßkomponenten* erklärt werden, welche das Erscheinungsbild der Hämophilie im Rahmen des Faktor IX-Mangels modifizieren. Diese Hypothese findet eine Bestätigung in dem von Shulmann, Smith, Erlandson, Fort und Lee (1956), Matter, Newcomb, Melly und Finch (1956) beschriebenen Bild der vaskulären Hämophilie. Achenbach und Kiefer (1957) bezeichnen dasselbe Krankheitsbild als Angiohämophilie. Die Autoren beschreiben Fälle mit schweren hämorrhagischen Diathesen bei einem relativ hohen Faktor VIII-Gehalt von 32–50%. Die Blutungszeit nach Duke war deutlich verlängert und betrug bis zu 12 Minuten, die Thrombozyten waren normal. Der geringfügige Mangel an

Faktor VIII, der allein das klinische Bild nicht erklären würde, wirkt sich hier also in Kombination mit einer vaskulär bedingten verlängerten Blutungszeit beträchtlich aus.

2. Die Konduktorinnen

Über das Verhalten der Blutungsbereitschaft bei heterozygoten Konduktorinnen sind die Meinungen immer noch geteilt. Frühere Autoren haben teilweise die Manifestation einer erhöhten Blutungsbereitschaft bei heterozygoten Konduktorinnen für möglich gehalten (SCHLOESSMANN, 1930). In solchen Fällen würde das hämophile Gen durch das gesunde X-chromosom nicht vollständig überdeckt werden und könnte mindestens teilweise zum Durchbruch gelangen. ANDREASSEN (1943) lehnte andererseits bei seinem Untersuchungsgut *klinische* Blutungserscheinungen bei Konduktorinnen als Manifestation des hämophilen Gens ab, da er sie als schwer objektivierbar beurteilt. Dagegen mißt er der Gerinnungszeit eine erhöhte Bedeutung zu.

Aber auch die neueren Untersuchungsergebnisse mit modernen gerinnungsphysiologischen Methoden haben bis heute noch nicht eindeutig die Frage gelöst. VERSTRAETE (1955) kommt bei seinen Untersuchungen zum Ergebnis, daß eine mögliche Konduktorin, welche einen Gehalt an antihämophilem Faktor von weniger als 50% aufweist, mit einer Wahrscheinlichkeit von 0,92 Trägerin eines hämophilen Gens ist. Andererseits haben MARGOLIUS und RATNOFF (1956) bei Hämophilie A unter 27 Konduktorinnen nur einen Fall von signifikant erniedrigtem Faktor VIII-Gehalt feststellen können.

Unsere Untersuchungen am Tenner Stamm mit Hämophilie B haben bei 11 sicheren und 32 möglichen Konduktorinnen weder klinisch noch gerinnungsphysiologisch irgendwelche sicheren Anhaltspunkte für eine erhöhte Blutungsbereitschaft, bzw. für einen erniedrigten Faktor IX-Gehalt ergeben. (Vgl. Tab. III und speziellen Teil der Arbeit MOOR-JANKOWSKI, TRUOG, HUSER, 1957.)

Immerhin weist die mögliche Konduktorin C X.620 einen Prothrombinverbrauch von 23% auf, was als pathologisch bezeichnet werden muß. Der Faktor-VIII-Gehalt ist normal, der Faktor IX-Gehalt beträgt 100%. Bei unserer Versuchsanordnung liegt die Fehlergrenze bei ±100%, d. h., die Streuung des Wertes von 100% reicht von 50–200%. Möglicherweise handelt es sich bei der Probandin doch um eine von VERSTRAETE (1957) postulierte, teilweise gerinnungsphysiologisch nachweisbare Manifestation des hämophilen Gens bei einer Konduktorin.

Bei den autosomal vererbten Koagulopathien ist die Frage der Konduktoren und Konduktorinnen eine grundsätzlich andere, wie wir oben bereits dargelegt haben.

III. Farbensehen

Projiziert man die drei Grundfarben des Spektrums, rot, grün und blau, auf einen Schirm, so daß sie sich überdecken, so empfindet ein normal Farbentüchtiger die dadurch entstehende Farbe als «weiß». Einen solchen Probanden bezeichnet man als *normalen Trichromaten*. Braucht er jedoch zur Empfindung «weiß» eine erhöhte Intensität einer der Grundfarben, so handelt es sich um einen *anomalen Trichromaten*. Die beiden Hauptgruppen dieser Farbsinnanomalie sind die *Protanomalie* oder Rotschwäche und die *Deuteranomalie* oder Grünschwäche.

Probanden, welche, um «weiß» zu erhalten, nur der Überdeckung zweier Farben bedürfen, bezeichnet man als *Dichromaten*, wobei man die beiden Hauptgruppen der *Protanopie* oder Rotblindheit und der *Deuteranopie* oder Grünblindheit unterscheidet.

Vereinzelt kann bei bestimmten Probanden eine entsprechende Intensität irgendeiner Farbe den Eindruck «weiß» erwecken. In diesem Fall handelt es sich um *Monochromaten* oder Totalfarbenblinde, welche die einzelnen Farben je nach Intensität nur als verschiedene Grautöne zu erkennen vermögen.

Farbsinnanomalien werden rezessiv geschlechtsgebunden vererbt. Es ist dabei noch nicht entschieden, ob Protanopie Protanomalie normal einerseits und Deuteranopie/Deuteranomalie normal andererseits je ein Allelpaar bilden, oder ob es sich um vier Allele auf ein und demselben Genlocus handelt (Stern, 1950). Im Hinblick auf die jedoch feststehende X-chromosomale Vererbung dieser Farbsinnanomalien und auf das ebenfalls X-chromosomal vererbte Hämophilie B-Gen im Bluterstamm von Tenna haben wir sämtliche in der Schweiz lebenden Bluter sowie ihre nächsten Angehörigen einer Farbsinnprüfung unterzogen. Dadurch sollten mögliche Genkoppelungen ermittelt und statistisch-genetisch verarbeitet werden.

a) *Methodik*

52 Probanden aus dem Stamm von Tenna wurden mittels der *Ishiharatafeln* auf Farbsinnanomalien geprüft.

Die Prüfung erfolgte durchwegs bei Tageslicht in normaler Lesedistanz von 30–40 cm. Als Stichzahlen wurden die Zahlen 29, 73, 5, 42 aus den wissenschaftlichen Tabellen Geigy (1955) verwendet. Zeigten sich dabei auch nur die geringsten Anhaltspunkte für eine Farbsinnanomalie, wurde dem betr. Probanden die ganze Serie der *Ishiharatafeln* vorgelegt, was jedoch in keinem der Fälle neue Ergebnisse gezeitigt hat. Kinder, welche noch nicht lesen konnten, wurden geheißen, den Linien nachzufahren. Wenn auch bei den Untersuchungen mit den *Ishiharatafeln* unter Umständen Versager eintreten können, wie

PICKFORD (1949, 1950) gezeigt hat, lassen sich die Überlegungen von PICKFORD, welche sich vor allem mit Farbsinnanomalien funktioneller Art befassen, nicht auf unser Untersuchungsgut übertragen, so daß wir die Ishiharamethode für unsere Untersuchungen für geeignet und genügend betrachten. Für die Beurteilung gelten folgende Richtlinien (aus GEIGY, wissenschaftliche Tabellen 1955):

Zahl 29: Der Trichromat liest 29, der Rot-Grün-Blinde oder Rot-Grün-Schwache liest die Zahl 70, der Totalfarbenblinde kann schwerlich eine Zahl lesen.

Zahl 73: Der Farbentüchtige liest 73, der Rot-Grün-Blinde oder Rot-Grün-Schwache kann schwerlich eine Zahl lesen.

Zahl 5: Der Farbentüchtige liest 5, der Rot-Grün-Blinde oder Rot-Grün-Schwache liest die Zahl 2, der Totalfarbenblinde kann schwerlich eine Zahl lesen.

Zahl 42: Der Farbentüchtige und der Rot-Grün-Schwache lesen 42, der vollkommen Rot-Blinde liest die Zahl 2, der vollkommen Grün-Blinde liest die Zahl 4.

b) *Ergebnisse*

Die Ergebnisse sind auf Tabelle IV dargestellt, wo gleichzeitig auch die Ergebnisse der CN-Geruchsinnprüfung angegeben werden. Die Zahlen werden in der Reihenfolge des Schemas angegeben, richtig gelesene Zahlen in Fettdruck. Weder bei den manifesten Blutern noch bei anderen Nachkommen aus dem Stamm von Tenna ließen sich Farbsinnanomalien feststellen. *Eine Koppelung des Hämophilie B-Gens mit einer Farbsinnanomalie liegt somit im Stamm der Bluter von Tenna nicht vor.*

IV. Cyanid-Geruchssinnprüfung

Die Tatsache, daß eine Anzahl Menschen, in erster Linie Männer, den Geruch von Blausäure nicht zu identifizieren vermögen, veranlaßte MOURANT 1950 zur Hypothese einer Geschlechtskoppelung. Untersuchungen auf Cyanid-Geruchssinnstörungen sind inzwischen von KIRK und STENHOUSE (1953), ALLISON (1953) und BÜCHI (1957) durchgeführt worden. Dabei fanden KIRK und STENHOUSE (1953) unter 132 Männern 24 und unter 112 Frauen 5 Probanden, die nicht in der Lage waren, die Blausäure vom Wasser dem Geruch nach zu unterscheiden. Diese Zahlen schienen auf eine X-chromosomale Vererbung des CN-Geruchsempfindens hinzuweisen.

Auf persönliche Anregung von Dr. A. E. MOURANT führten wir bei 50 Nachkommen aus dem Stamm der Bluter von Tenna eine Geruchssinnprüfung mit Cyanid durch. Unter den Probanden fanden sich 9 Bluter.

a) *Methodik*

Unsere Untersuchungstechnik entsprach derjenigen von KIRK und STENHOUSE (1953), ALLISON (1953) und BÜCHI (1957):

Tab. IV. Ergebnisse der Farbsinn- und der CN-Geruchssinnprüfung bei den Nachkommen aus dem Bluterstamm von Tenna

| Standortnummer | | Farbsinnprüfung (Testzahlen 29, 5 ,73, 42) | | CN-Geruchssinnprüfung (Testproben 3, 5, 8, 9) | | Gerinnungsstatus | |
		Ergebnis	Bewertung	Ergebnis	Bewertung	Durchgeführt	Ergebnis
B X. 444	♀	29 5 73 42	Trichromat	2 3 8	Nichtriecher	+	−
450	♀	29 5 73 42	Trichromat	3! 5 8 9	Riecher	+	−
456	♀	29 5 73 42	Trichromat			+	
459*	♂			3 8 5	Riecher		
460	♀	29 5 73 42	Trichromat	2 3 5	Nichtriecher	+	−
464	♂	29 5 73 42	Trichromat	0 0 0 0	Nichtriecher	+	Hämophilie
465*	♀	29 5 73 42	Trichromat	9 3 5	Riecher		
467	♀	29 5 73 42	Trichromat	0 0 0 0	Nichtriecher	+	
478	♂	29 5 73 42	Trichromat	0 0 0 0	Nichtriecher	+	Hämophilie
479*	♀	29 5 73 42	Trichromat	3 9 10 5	Riecher		
481	♀					+	−
482	♂	29 5 73 42	Trichromat	3 5 8 9	Riecher	+	Hämophilie
483*	♀	29 5 73 42	Trichromat	3 8	Nichtriecher(?)		
484*	♂			0 0 0 0	Nichtriecher		
485	♀	29 5 23 42	Trichromat	0 0 0 0	Nichtriecher	+	−
490	♀	29 5 73 42	Trichromat			+	
491	♂	29 5 73 42	Trichromat	0 0 0 0	Nichtriecher	+	−
493	♀					+	
496	♂			3	Nichtriecher		
497	♀	29 5 73 42	Trichromat	8 5! 10 3	Riecher	+	−
B XI. 449	♂	29 5 73 42	Trichromat			+	−
450	♀					+	−
456	♂	29 5 73 42	Trichromat	5 9 0 0	Nichtriecher		
457	♀	29 5 78 42	Trichromat				
458	♂	29 5 78 42	Trichromat	2 8 5 3	Riecher	+	Hämophilie
461	♂	29 5 73 42	Trichromat	8 9 3 2 4	Riecher		
462	♀	29 5 73 42	Trichromat	5 2	Nichtriecher	+	−
463	♀	29 5 73 42	Trichromat			+	
464	♀	29 5 73 42	Trichromat	3 8 5	Riecher	+	−
465	♀	20 5 73 42	Trichromat			+	−
466	♂	29 5 73 42	Trichromat	5 8 9+ 3	Riecher	+	Hämophilie
478	♀	29 5 73 42	Trichromat			+	
479	♀			5 3 9 8	Riecher	+	
480	♂			3 1 10 8	Nichtriecher	+	−
481	♂			8 3 9	Riecher	+	−
482	♀					+	−
B XI. 483	♀					+	−
484	♂					+	−
485	♂					+	−
486	♂	29 5 73 42	Trichromat	2 3 4 8 9	Riecher		
488	♂	20 5 13 42	Trichromat	4 5 8+	Riecher	+	−
489	♂	20 5 73 42	Trichromat	3 5 8 9	Riecher	+	Hämophilie
490	♂	20 5 73 42	Trichromat	1 9	Nichtriecher	+	−
493	♀					+	−
494	♀					+	−
495	♀					+	−
496	♀					+	−
497	♀					+	−
499	♀					+	−
505	♂	29 5 73 42	Trichromat	1 3 2 9 10	Nichtriecher	+	Hämophilie
506	♀	20 5 73 42	Trichromat	2 1 8 5	Nichtriecher	+	−
507	♂	29 5 73 42	Trichromat	5 9 4 3	Riecher	+	Hämophilie

Tab. IV. Ergebnisse der Farbsinn- und der CN-Geruchssinnprüfung bei den Nachkommen aus dem Bluterstamm von Tenna

Standortnummer		Farbsinnprüfung (Testzahlen 29, 5, 73, 42)		CN-Geruchssinnprüfung (Testproben 3, 5, 8, 9)		Gerinnungsstatus	
		Ergebnis	Bewertung	Ergebnis	Bewertung	Durch-geführt	Ergebnis
X. 601	♀					+	–
607	♀	29 5 73 42	Trichromat			+	–
610	♀	29 5 73 42	Trichromat			+	–
612	♀	29 5 73 42	Trichromat	4 5 9	Nichtriecher	+	–
613*	♂	29 5 73 42	Trichromat	1 3 5	Nichtriecher		
614	♀	29 5 73 42	Trichromat	3 9	Nichtriecher	+	
627	♂			3 5 9 8	Riecher		
629	♀	29 5 73 42	Trichromat	2 3 9	Nichtriecher	+	–
XI. 643	♀					+	–
648	♂	29 5 73 42	Trichromat			+	Hämophilie B
650*	♂			5	Nichtriecher		
651	♀			3	Nichtriecher		
654	♀	29 5 73 42	Trichromat	8 3 9 5	Riecher	+	–
657	♂	29 5 73 42	Trichromat			+	Hämophilie B
659	♀					+	–
660	♀					+	–
663	♀					+	–
664	♀					+	–
666	♀	29 5 73 42	Trichromat	1 3 2 9	Nichtriecher	+	–
667	♀	29 5 73 42	Trichromat	5 9 8+	Riecher		
669	♂	29 5 73 42	Trichromat	3 8 5 10	Riecher	+	–
671	♀	29 5 73 42	Trichromat	8+ 5 3 9	Riecher	+	–
673	♀	29 5 73 42	Trichromat	5 9 8	Riecher	+	–
XII. 177	♀					+	–
178	♀					+	–
183	♂	29 5 73 42	Trichromat	9 8 5 3	Riecher	+	–
184	♀	19 5 73 42	Trichromat	1 10 5!!	Riecher		
185	♂	29 5 73 42	Trichromat	1 2 10 9	Nichtriecher		
186	♀	29 5 73 42	Trichromat	10 9 2 5	Nichtriecher		
187	♂						
188	♀					+	–
189	♂					+	–
190	♂					+	–
191	♂	20 5 73 42	Trichromat	5	Nichtriecher	+	–

Anmerkungen zu Tab. 4

Kolonne Standortnummer: Fettdruck bedeutet klinisch oder gerinnungsphysiologisch manifester Bluter. Mit * bezeichnete Probanden sind nur im Namenverzeichnis, nicht aber in der Nachfahrentafel (Acta Genetica 7, 4, 57) verzeichnet.

Farbsehprüfung: Unter Ergebnis werden sämtliche von den Probanden anhand der Testzahlen genannten Zahlen erwähnt, richtige Zahlen in Fettdruck.

CN-Geruchssinnprüfung: Unter Ergebnis werden sämtliche von den Probanden als Geruchstoff enthaltende Fläschchen angegeben, richtig bezeichnete Fläschchen in Fettdruck. Richtig beschriebene Geruchsqualität (bittere Mandeln, Nüsse usw.) werden mit +, starke subjektive Reaktion mit !, unsichere Beurteilung mit ? vermerkt. Zahlen in Reihenfolge der Bestimmung angeordnet.

Die geringfügigen Unterschiede der Zahl der untersuchten Probanden dieser Tabelle und der Probandenzahl in Acta Genetica 7, 4, 1957 beruhen auf hier noch mitberücksichtigten Nach- und Kontrolluntersuchungen.

Vier verschlossene Fläschchen enthielten eine 20% Lösung von analysenreinem Kaliumcyanid (Fabrikmarke «Analar»), und vier gleiche Fläschchen enthielten destilliertes Wasser. Die Fläschchen trugen die Nummern 1, 2, 3, 4, 5, 8, 9, 10. Durch Los wurden die Nummern 3, 5, 8, 9 bestimmt und die Fläschchen mit Kaliumcyanid gefüllt, die Fläschchen mit den übrigen Nummern enthielten destilliertes Wasser. Diese Flaschen mußten von den Probanden richtig in zwei Gruppen geschieden werden. Der normale Geruchsinn der Probanden wurde vorerst mit aqua laurocerasi Pharmacopea Helvetica V geprüft, einem Geschmackskorrigens mit aromatischem Geruch. Die Auswertung der so erhaltenen Ergebnisse war oft recht schwierig, indem die Probanden nur selten ganz einwandfrei alle 4 Fläschchen zu erkennen vermochten. Bei starken Riechern blieb der Geruch des Cyanids bereits nach dem ersten Fläschchen an den Rezeptoren der Nasenschleimhaut haften, so daß die folgenden Proben oft nicht mehr differenziert werden konnten. Schwache Riecher kamen infolge des bei ihnen länger dauernden Versuchs mit einer größeren Dosis KCN in Berührung und wurden im Verlauf des Testes oft leicht benommen, was wiederum die Differenzierung der weiteren Proben erschwerte.

Andererseits zeigte sich aber auch eine gewisse Protraktion der Wirkung des Riechstoffes, indem er bei einigen Probanden erst nach der zweiten oder dritten Probe die Reizschwelle der Rezeptoren erreichte.

Bei der Auswertung der Ergebnisse haben wir deshalb anhand unserer Protokolle nebst den objektiven auch die subjektiven Angaben gewertet.

Als Riecher wurden bezeichnet:

1. Probanden, welche einwandfrei 3 Fläschchen richtig bezeichneten;

2. Probanden, welche beim ersten Cyanidfläschchen subjektiv stark reagierten, auch wenn sie weniger als 3 Fläschchen richtig identifizieren konnten;

3. Probanden, welche bei einem der Cyanidfläschchen spontan den Geruch einigermaßen richtig beschrieben (bittere Mandeln, Nüsse usw.), auch wenn sie weniger als 3 Fläschchen richtig identifizieren konnten.

b) *Ergebnisse*

In Tabelle 4 werden die Nummern der gewählten Fläschchen angegeben, richtig bestimmte Nummern in Fettdruck. Subjektiv stark empfundener Geruch wird bei der entsprechenden Nummer mit ! vermerkt, richtige Umschreibung der Geruchsqualität mit +.

Dazu läßt sich zusammenfassend vorerst sagen, daß in unserem Material bei den Männern auf 13 Nichtriecher 13 Riecher kommen, bei den Frauen 11 Riecherinnen auf 13 Nichtriecherinnen.

Diese Werte sind stark von den Ergebnissen früherer Autoren verschieden, indem Kirk und Stenhouse 18,2% Nichtriecher, Allison 25,4% und Büchi 18,4% fanden.

Die Gründe für diese Differenzen liegen unseres Erachtens in der Tatsache, daß es sich bei unserem Material um Familienuntersuchungen han-

delt und somit ein Großteil der Probanden untereinander verwandt sind. Dadurch sind die Verhältnisse statistisch nicht mehr vergleichbar. Ferner besteht eventuell die Möglichkeit, daß frühere Autoren nicht analysenreine Substanzen verwendet haben. Bereits geringgradige Verunreinigungen wirken sich auf die Geruchsintensität beträchtlich aus.

Das Ergebnis unserer Familienuntersuchungen im Bluterstamm von Tenna haben wir zu kleinen Stammbäumen zusammengefaßt.
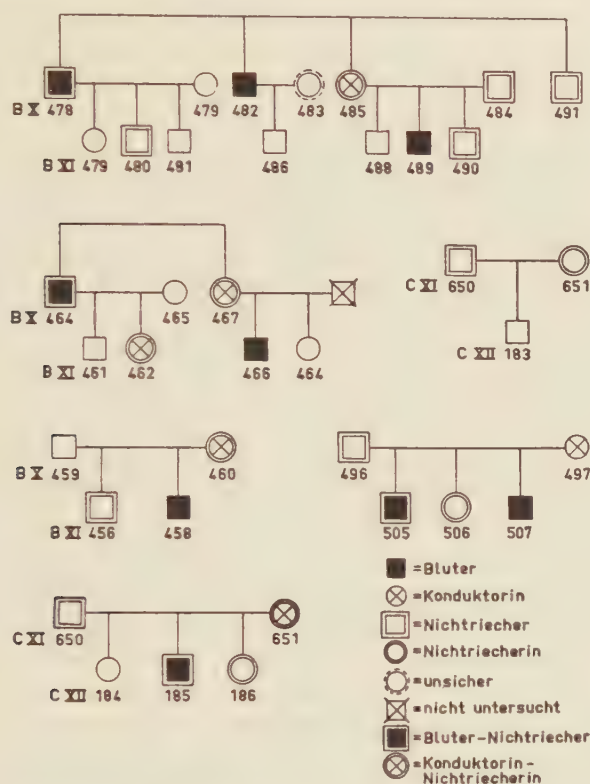
Abb. 6. Übersicht über die Ergebnisse der CN-Geruchssinnprüfungen der Nachkommen aus dem Stamm der Bluter von Tenna.

Daraus lassen sich folgende Schlußfolgerungen ziehen:

1. Die Vererbung einer CN-Geruchssinnanomalie erfolgt nicht rezessiv.

2. Die Vererbung einer CN-Geruchssinnanomalie erfolgt nicht geschlechtsgekoppelt, eine Koppelung mit dem Hämophilie B-Gen im Stamm von Tenna ist auszuschließen.

3. Soweit das nur kleine Material schlüssig ist, würde die Vererbung dominant erfolgen. Eine absolute Geschlechtskoppelung kann dabei ausgeschlossen werden, eine partielle Geschlechtskoppelung ist nicht ausschließbar, da wir in keinem Fall drei vollständig untersuchte Probandengenerationen haben.

Zusammenfassung

Die erblichen Formen der Koagulopathien werden diskutiert und im Hinblick auf die Vererbung der entsprechenden Gerinnungsfaktoren unter Quellenangabe tabellarisch zusammengestellt. Den wahrscheinlich autosomalen, teils dominanten, teils rezessiven und teils intermediären Erbgängen der meisten Koagulopathien lassen sich die rezessiv geschlechtsgebundenen Erbgänge der klassischen Hämophilien A und B gegenüberstellen. – Anhand der Untersuchungen am Hämophilie B-Stamm der Bluter von Tenna wird sodann die Frage der gerinnungsphysiologischen und klinischen Manifestation des Hämophilie B-Gens erörtert. Es wurden 67 Probanden aus dem Bluterstamm von Tenna gerinnungsphysiologisch geprüft, darunter 10 Bluter und 11 sichere Konduktorinnen; alle Bluter und Konduktorinnen wurden klinisch und anamnestisch untersucht. Gerinnungsphysiologisch weisen die *Bluter* nur geringe Unterschiede im Faktor IX-Gehalt auf (2,5–6% der Norm) in der klinischen Manifestation dagegen zeigen sich ausgeprägte Verschiedenheiten in Grad und Erscheinungsform der Krankheit. Ein Bluter mit einem Faktor IX-Gehalt von 2,5% ist klinisch nicht manifest; in den meisten Anamnesen zeigt sich eine Abnahme der Blutungsneigung mit dem Alter. Die *Konduktorinnen* weisen klinisch keine erhöhte Blutungsneigung und gerinnungsphysiologisch keine sicheren Anhaltspunkte einer Koagulopathie auf. Immerhin zeigt eine mögliche Konduktorin eine gesichert pathologische Prothrombinconsumption. – Die Farbsinnprüfungen ergaben bei 52 Probanden, darunter 11 Blutern, keine Koppelung von Daltonismus mit Hämophilie B. – Die Cyanidgeruchssinnprüfung ergab bei 50 Probanden, darunter 9 Blutern, einen dominanten, wahrscheinlich autosomalen Erbgang. – Die Methodik der gerinnungsphysiologischen Untersuchungen sowie die Methodik der Untersuchungen auf Farbsinn – und CN – Geruchssinnanomalien werden im einzelnen beschrieben und die Resultate tabellarisch zusammengefaßt.

Summary

The inherited forms of disturbances of blood coagulation are discussed. A tabular presentation of the corresponding coagulatory factors and the

literature in respect to the inheritance is given. The autosomal, partially dominant, partially recessive and partially intermediary processes which constitute probably most of the disturbances in coagulation are contrasted with the recessive sex-linked hereditary processes of the classical hemophilias A and B. – On the basis of examinations of the hemophilia B sibling from the hemophiliacs of Tenna, the question of coagulation physiology and the clinical manifestation of the hemophilia B gene is discussed. 67 individuals from the Tenna siblings were examined with respect to coagulation physiology, among whom there were 10 bleeders and 11 carriers. Both the bleeders and the carriers were examined clinically and anamnestically. Regarding physiology of coagulation, the *bleeders* showed only a small difference in the amount of factor IX deficiency (2,5–6% of normal); clinically, however, they showed marked differences in the severity of the disease and the form in which it manifested itself. One bleeder with a factor IX concentration of 2,5% does not manifest himself clinically. In the usual case histories, a decrease in the bleeding tendency is noted with increasing age. The *carriers* showed clinically no increased tendency to bleeding; they neither demonstrated a disturbance in relation to the physiology of their coagulatory mechanisms. Nevertheless, a potential carrier did show a definitely pathological prothrombine consumption test. – An examination of the color sense of 52 individuals, of whom 11 were bleeders, showed no coupling of Daltonism with hemophilia B. – An examination of the ability to smell cyanide solutions performed in 50 individuals, 9 of whom were bleeders, showed a dominant, probably autosomal inheritance process. – The method used in studying the physiology of coagulation as well as the methods for testing color vision and the ability to smell cyanide are described and the results given in tabular form.

Résumé

Les auteurs discutent les formes héréditaires des troubles de la coagulation du sang qu'ils résument en un tableau en fonction de leur caractère héréditaire. Ils opposent l'hérédité récessive et liée au sexe des hémophiles classiques A et B aux formes probablement autosomales dominantes, récessives ou intermédiaires de la grande majorité des troubles de la coagulation. – Ils exposent les examens effectués chez les sujets de la souche hémophile B de Tenna, ainsi que les troubles de la coagulation et les manifestations cliniques de l'hémophilie B. Ils étudient les facteurs de coagulation de 67 sujets issus de la souche hémophile de Tenna parmi lesquels 10 hémophiles et 11 conductrices certaines. Chez ces derniers ils procédèrent

à des recherches anamnestiques et à un examen clinique détaillés. Chez les *hémophiles* le teneur en facteur IX oscille entre 2,5 et 6% de la valeur normale et ne montre donc que peu de variations, alors que les manifestations cliniques de la maladie sont aussi diverses dans leur gravidité que dans leur forme. Un hémophile présente un taux de facteur IX à 2,5% sans aucune symptomatologie clinique. La plupart des cas voient avec l'âge une diminution de la tendance aux hémorrhagies. Cliniquement les *conductrices* ne manifestent pas de tendance aux hémorrhagies et l'examen des facteurs de la coagulation ne permet pas d'affirmer l'existence d'un trouble de la coagulation. Une conductrice possible présente un «Prothrombinconsumption test» pathologique. – Chez 52 sujets dont 11 hémophiles l'examen de la discrimination des couleurs ne révèle pas de Daltonisme lié à l'hémophilie B. – L'examen de l'odorat au Cyanid met en évidence chez 50 sujets dont 9 hémophiles une hérédité dominante probablement autosomale. – Les techniques des examens de la coagulation, de la recherche des anomalies de perception des couleurs et de l'examen de l'odorat par le Cyanid sont décrites en détail. Les résultats sont résumés par des tableaux.

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THE MONOGENIC THEORY OF SCHIZOPHRENIA

By ELIOT SLATER

Despite the researches of thirty years, the genetic basis of schizophrenia still remains a matter of doubt. Some of the available observations suggest a recessive mode of inheritance, while others are more easily reconciled with dominance. To explain the discrepancies it has been suggested that schizophrenia is genetically heterogenous; but even this attempt to make the best of both worlds encounters difficulties.

In his important paper on a North Swedish population, *Böök* (1953) proposed the hypothesis that, in this population isolate, schizophrenia was due to a recessive gene which manifested itself in all homozygotes and in

about one in every five heterozygotes. This was, in fact, the hypothesis which provided the best fit for his data. It is one which involves features both of dominance and recessivity; and it is desirable to see whether hypotheses of this form might be compatible with the data obtained from other populations, whether, in fact, the monogenic theory of *Böök* could be applied more universally.

Böök's calculations of the frequencies of genotypes and matings are not very easy to follow; and as an alternative approach the following simple formulation is offered. We shall write A = the dominant (normal) gene, with frequency of $(1-p)$ in the population, and a = the schizophrenic gene, with frequency p. Then among the relatives of particular genotypes, other named genotypes will appear with frequencies which will be functions of p, as shown in the following table.
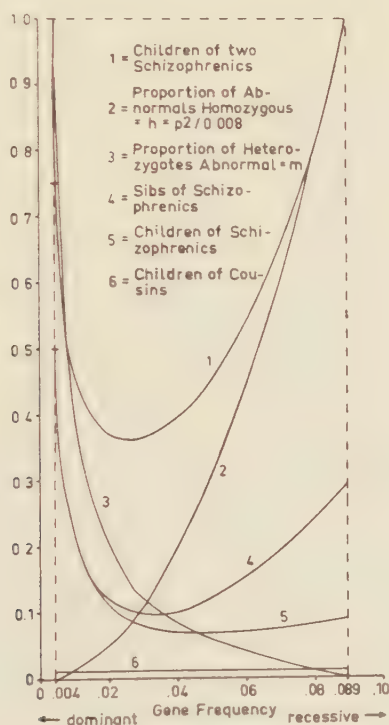
The frequency of schizophrenia in the general population (s) is given by the formula $s = 2mp(1-p) + p^2$, where m is the frequency of manifestation of the schizophrenic gene in the heterozygote. We can take 0.008 as a fairly reliable estimate of the frequency of schizophrenia in most European

Table 1

| Relative | of Genotype | will be | with Frequency as Coefficients of | | |
			p^0	p^1	p^2
Parents	AA	AA	+1	—1	
and		Aa		+1	
Children	Aa	AA	+1/2	—1/2	
		Aa	+1/2		
		aa		+1/2	
	aa	Aa	+1	—1	
		aa		+1	
Sibs	AA	AA	+1	—1	+1/4
		Aa		+1	—1/2
		aa			+1/4
	Aa	AA	+1/2	—3/4	+1/4
		Aa	+1/2	+1/2	—1/2
		aa		+1/4	+1/4
	aa	AA	+1/4	—1/2	+1/4
		Aa	+1/2		—1/2
		aa	+1/4	+1/2	+1/4
Children of First Cousins		AA	+1	—31/16	+15/16
		Aa		+30/16	—30/16
		aa		+ 1/16	+15/16

countries. Using this formula, we can calculate the value of p corresponding to every value of m between its limits of 0 and 1, or, more conveniently, calculate the value of m corresponding to various values of p. It is also interesting to note at the same time the corresponding values of h, where $h = p^2/0.008$, and represents the proportion of all schizophrenics who are homozygotes. This is a convenient measure of the degree to which the mode of inheritance approaches to recessivity, and varies between 1 and a very small value.

To every value of p, and of m, there will also correspond values for the expectation of schizophrenia among the various classes of relatives of schizophrenics, or in given types of matings. There are available the results of adequate investigations of the frequency of schizophrenia in the children of schizophrenics, in their sibs, and in the children of two schizophrenic consorts. Furthermore, *Nixon* and *Slater* (1957) have made one estimate of the frequency of schizophrenia in the children of first cousins. The theoretical expectations, calculated by the use of Table 1, are as follows:

Frequency of schizophrenia in the children of schizophrenics

$$= {}^1\!/_2 (1+h) (m+p) - hmp;$$

Frequency of schizophrenia in the sibs of schizophrenics
$$= \tfrac{1}{4} \{2m+h+p\,(2m+h+1-2mh)+p^2\,(1-2m)\};$$

Frequency of schizophrenia in the children of two schizophrenics
$$= \tfrac{1}{4}\,(1+h)\,\{2m\,(1-h)+1+h\};$$

Frequency of schizophrenia in the children of first cousins
$$= \tfrac{1}{16}\,(15s+p).$$

Values of these expectations have been calculated for eleven points of the entire range of possibilities, and are given in the following table.

Table 2

p	m	h	Sibs	Ch of 1	Ch of 2	Ch of cousins
$(.008)^{1/2}$ $=.0894$	0.0000	1.0000	0.2967	0.0894	1.0000	0.0131
0.080	0.0109	0.8000	0.2431	0.0811	0.8120	0.0125
0.070	0.0238	0.6125	0.1947	0.0735	0.6575	0.0119
0.060	0.0390	0.4500	0.1552	0.0707	0.5412	0.0113
0.050	0.0580	0.3125	0.1239	0.0699	0.4568	0.0106
0.040	0.0833	0.2000	0.1053	0.0733	0.4000	0.0100
0.030	0.1219	0.1125	0.0993	0.0841	0.3696	0.0094
0.020	0.1939	0.0500	0.1166	0.1121	0.3723	0.0088
0.015	0.2631	0.0281	0.1444	0.1429	0.3957	0.0084
0.010	0.3990	0.0125	0.2071	0.2070	0.4558	0.0081
0.004	1.0000	0.0020	0.5034	0.5030	0.7510	0.0078

The relationships between p, m and h and the corresponding expectations of schizophrenia in the various classes of relative are also shown in the figure. This makes very evident the extent to which the expectation in the sibs drops between the extremes of recessivity and dominance, instead of taking, as one might have expected, intermediate values; the minimum is seen in the neighbourhood of the point where there is a 12 per cent rate of manifestation in the heterozygote. Something similar is seen in the behaviour of the figures for the children of one schizophrenic, where the minimum is found at a 6 per cent rate of manifestation; but there is very little change between the 12 per cent point and the extreme of absolute recessivity. At low gene frequencies, when m exceeds 0.2, there is practically no difference between the expectations in sibs and in children. It is also noteworthy that the expectation of schizophrenia in the children of two schizophrenics varies in a remarkable way between the extremes

of dominance and recessivity, so that observational estimates are clearly capable of providing valuable information. The expectation of schizophrenia in the children of cousins, on the other hand, varies very little and shows itself to be an insensitive measure of dominance-recessivity.

We may now compare the expectations with the frequencies that have been actually observed. The frequency of schizophrenia in the sibs of schizophrenics has been estimated by *Kallmann* (1953) as 0.142; other workers have found a slightly lower figure. This expectation is found on the curve for sibs both at gene frequency 0.015 and again at 0.055. If the frequency were lower than 0.142, a corresponding expectation could be found with a *p* value between these limits. *Kallmann*, again, has found the frequency of schizophrenia in the children of schizophrenics to be 0.164; this point is found on the curve for children at gene frequency 0.013. The estimate of *Elsässer* (1952) for the frequency of schizophrenia in the children of two schizophrenic consorts is 0.392. This point is found on the corresponding curve at values of *p* of 0.015 and 0.038. Finally, *Nixon* and *Slater* estimated that the frequency of schizophrenia in the children of cousins was 57/40 of the frequency in the general population = 0.011, which corresponds with a gene frequency of 0.055.

When one takes into account the magnitude of the statistical errors to which all these estimates are liable, it is seen that they are all readily compatible with a gene frequency of about 0.015, and a manifestation rate in the heterozygote of about 0.26. At this point, all but 3 per cent of schizophrenics are heterozygous.

There is one important group of observations of which so far no mention has been made, i.e. the data relating to the incidence of schizophrenia in the MZ twins of schizophrenics. The concordance rate within MZ pairs has been estimated as lying between 76 per cent (*Slater*, 1953) und 86 per cent (*Kallmann*). If we merely thought of the MZ co-twins of schizophrenics as a group of persons of whom 3 per cent were homozygous and 97 per cent were heterozygous, then we might conclude that the concordance rate should be 28 per cent. However, the MZ co-twins of schizophrenics are identical with their partners, not only in respect of the hypothetical specific schizophrenic gene, but also in respect of the total genetic equipment. If a much higher concordance rate than 28 per cent is actually found, this is a matter for no surprise. But the fact that the genotypic milieu should play such a part deprives the data obtained from twins of any value for the testing of the monogenic hypothesis.

If it were desired, it would be a simple though slightly laborious task to calculate expectations for other classes of relatives than those discussed

above. It seems improbable, however, that information of much critical value would be thereby obtained. Furthermore, the observational data for comparison would be less reliable. In the case of one class, that of parents, the observed frequency of schizophrenia could not be safely used for such a purpose, since parents are a group of persons who have been selected for survival and for health.

Taking the material we have, it would seem that some at least of our knowledge of the incidence of schizophrenia in the relatives of schizophrenics could be adequately explained by the hypothesis of a single partially dominant gene, such as *Böök* proposed for the special circumstances of a North Swedish isolate; and that this hypothesis therefore merits further investigation.

Summary

The consequences are examined of a hypothesis which proposes a single partially dominant gene as the genetical basis of schizophrenia. It is shown that a simple relationship connects gene frequency and rate of manifestation in the heterozygote, if the frequency of schizophrenia in the general population is held constant; a series of values for these two variables has been calculated, when the frequency of schizophrenia is taken as 0.008. The expectation of schizophrenia in certain classes of relatives of schizophrenics also varies with the gene frequency and with the manifestation rate, but in a complex way such that, between high values at the extremes of complete dominance and complete recessivity, not intermediate values but minima are found. The observed frequencies of schizophrenia in the sibs of schizophrenics, in the children of one schizophrenic parent, and in the children of two schizophrenic parents, are compatible with this theory, and would correspond with a manifestation rate in the heterozygote of about 0.26 and a gene frequency of about 0.015.

Zusammenfassung

Es wird untersucht, welche Konsequenzen sich aus einer Hypothese ergeben, die ein einfaches, unvollständig dominantes Gen als genetische Grundlage der Schizophrenie annimmt. Dabei läßt sich eine einfache Beziehung zwischen Genhäufigkeit und Manifestationswahrscheinlichkeit bei den Heterozygoten aufzeigen, wenn man die Häufigkeit der Schizophrenie

in der Bevölkerung konstant hält. Für eine Häufigkeit dieser Krankheit von 0,008 wird eine Reihe von Werten für diese beiden Variablen errechnet. Auch die Erwartungswerte für die Schizophrenie-Häufigkeit in bestimmten Gruppen von Verwandten der Patienten ändert sich mit Genhäufigkeit und Manifestationswahrscheinlichkeit; diese Änderung ist jedoch ein komplexes Phänomen, was zur Folge hat, daß man zwischen hohen Werten bei den Extremen vollständiger Dominanz und vollständiger Rezessivität nicht dazwischen liegende Werte, sondern Minima erhält. Die beobachtete Häufigkeit von Schizophrenie bei Geschwistern von Kranken, bei Kindern eines schizophrenen Elternteils und bei Kindern zweier befallener Eltern sind mit dieser Theorie verträglich; man kann eine Manifestationswahrscheinlichkeit von ungefähr 0,26 bei den Heterozygoten und eine Genhäufigkeit von etwa 0,015 annehmen.

Résumé

L'auteur s'occupe des conséquences d'une hypothèse admettant que la base génétique de la schizophrénie soit un seul gène partiellement dominant. Il montre qu'il existe une relation directe entre la fréquence du gène et la manifestation dans l'état hétérozygote, si la fréquence de la schizophrénie dans la population en général est considérée comme constante; une série de valeurs pour ces deux variables a été calculée en se basant sur une fréquence de la schizophrénie de 0,008. La probabilité pour la schizophrénie d'apparaître chez les parents des malades varie également avec la fréquence du gène et du taux de manifestations, mais d'une manière très complexe et ceci de façon telle qu'on ne trouve entre les valeurs extrêmes pour une dominance et une récessivité complètes pas de valeurs intermédiaires, mais uniquement des minima. La fréquence observée de la schizophrénie dans les familles des probants, chez les enfants dont un des parents ou les deux parents sont schizophrènes concorde avec cette hypothèse et correspond à un taux de manifestations chez l'hétérozygote d'environ 0,26 et à une fréquence du gene d'environ 0,015.

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THE ELECTROENCEPHALOGRAM
IN UNIOVULAR TWINS BROUGHT UP APART

By N. JUEL-NIELSEN and B. HARVALD

The observation that the EEG patterns in both partners in uniovular twins may be surprisingly alike was first made by *Davis* and *Davis* [1936]. This finding was confirmed later by several investigators, primarily by *Lennox, Gibbs* and *Gibbs* [1945] who found practically identical EEGs in 47 pairs in a series of 55 uniovular pairs of twins, and significant differences in 18 out of 19 binovular pairs. In an extensive study *Vogel* [1956] analyzed various electroencephalographic traits in 208 pairs of twins and found an amazingly good agreement in uniovular twins. *Raney* [1939] demonstrated mirror imaging in the EEG where the dominant hemisphere was concerned in some of his pairs of twins.

This pronounced similarity between EEG findings in uniovular twins when contrasted with the corresponding dissimilarity between binovular twins, may be regarded as evidence of the hereditary nature of the EEG pattern. The argument may be raised, however, that the environmental conditions both in their physical and mental aspects are, as a rule, much more uniform where uniovular twins are concerned than in the case of binovular twins. The possibility that the similarity in EEG patterns found in uniovular twins by the ordinary twin method is primarily due to similarities in their mutual environment during the years of growth, cannot be dismissed a priori.

This question may be decided on a basis of EEG studies in uniovular twins who have grown up each in a different environment. No accounts have hitherto appeared in the literature concerning such an EEG investigation in separated uniovular twins.

Table 1. EEG in 8 Pairs of Uniovular Twins Brought up Apart

No.	Sex	Age years	Clinical traits	Dominant activity		Range[2]	Response to		Abnormal traits
				frequency[1] per sec.	voltage[1] microvolt		hyperventilation	flicker lamp	
I	male	22	1) –	11	50	++	0		5 per sec. activity (occipital)
			2) enuresis febrile convulsions in infancy	11	50	+++	0		5 per sec. activity (occipital)
II	female	37	1) –	9	75	++++	voltage increased	voltage suppressed	6 per sec. activity (frontal)
			2) enuresis	9–10	75	+++++	voltage increased	voltage suppressed	0
III	female	42	1) –	9–10	75	++	voltage increased		0
			2) –	9–10	75	++	voltage increased		0
IV	male	46	1) enuresis	10	120	++++	0		0
			2) –	10	70	+++++	0		0
V	female	49	1) hemicrania	8–9	120	++		voltage increased	0
			2) hemicrania left-handed	10	120	++++		voltage increased	0
VI	female	56	1) el.-shock treatment	10	75	++	0		small 8 per sec. paroxysms
			2) –	10	75	++++	0		small 8 per sec. paroxysms
VII	female	71	1) left-handed	9–10	50	+			0
			2) –	9–10	50	++			0
VIII	female	72	1) –	9–11	50	+++			0
			2) –	9–11	50	+++			0

[1] measured in right occipital region.

[2] measured in right occipital region. + = 0–25% of total period of registration, ++ = 25–50%, +++ = 50–75%, ++++ = 75–100%.

Over a period of years, one of the authors (J.-N.) undertook the collection of Danish material of uniovular pairs of twins who have grown up apart. The twins were adopted separately or placed in separate foster homes shortly after birth; in an isolated case as early as the day after birth. In the majority of cases the twin partners were not re-united until in adult life, frequently after having experienced very varied modes of life which had widely separated them socially from each other.

The diagnosis of uniovularity in the material is primarily based upon a series of comprehensive investigations of blood groups (in 8 systems) and haptoglobin types.

Eight of these uniovular twin pairs who had grown up apart were investigated electroencephalographically. The results are presented in Table 1.

For a description of the EEG, various qualities were evaluated and compared. The *frequency* of the dominant activity was measured occipitally. The *amplitude* of the dominant activity was similarly measured and calculated as the average amplitude of the dominant activity in the right occipital region measured in the standard lead (right occipital–right ear). This figure can naturally only be an approximation. The *distribution in time* of the dominant activity was calculated as a percentage of the total period of EEG recording, similarly in the right occipital region. In 5 pairs, provocation tests were undertaken with hyperventilation for 3 minutes, and in 2 pairs with a flickering lamp. The effects of these provocation tests are compared.

None of the pairs of twins investigated had shown any definite epileptic symptoms. In one pair, one of the twins (I_2) had been admitted to hospital in infancy on account of transient and uncharacteristic seizures and suffered, in addition, from enuresis until the age of 12 while the twin brother never showed such symptoms. In 2 other pairs, one of the twins (II_2 and IV_1) had enuresis in childhood while the other had not. Among other clinical findings which might be relevant for the EEG it may be mentioned that both twins in one pair (V) had pronounced typical migraine which had been present since childhood in both. The twin VI_1 had received a series of 8 electroshock treatments during a period 10–6 weeks prior to the EEG investigation.

The investigation has not yet been concluded as regards the psychiatric and psychological conditions and no attempt has been made to correlate these with the EEG.

In Figures 1–8 representative periods of the EEG for the twin pairs are demonstrated.

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EEG of 8 pairs of uniovular twins brought up apart. In all cases standard lead: left frontal–left ear, right frontal–right ear, left occipital–left ear, right occipital–right ear. Order of succession is the same as that used in Table 1.
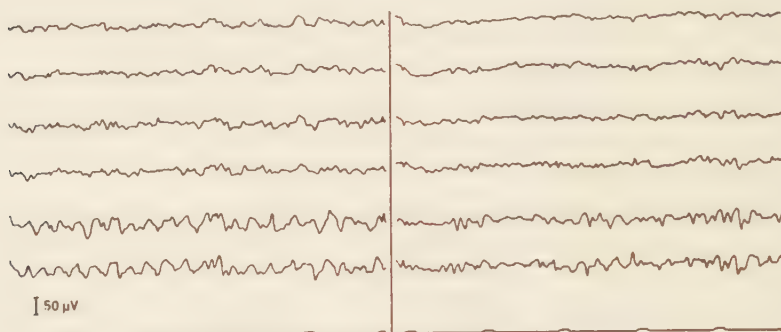
Fig. 1. Male twins, aged 22.
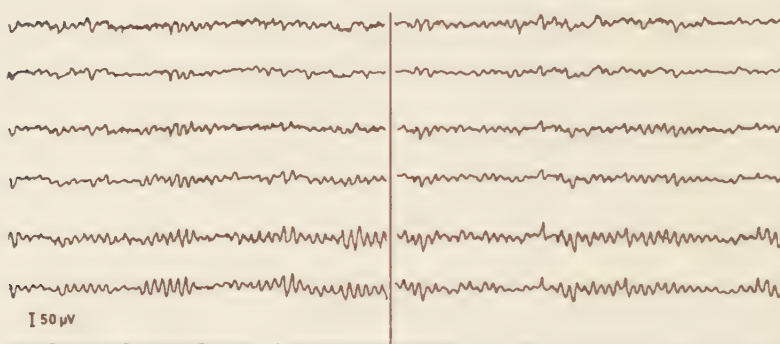
Fig. 2. Female twins, aged 37.
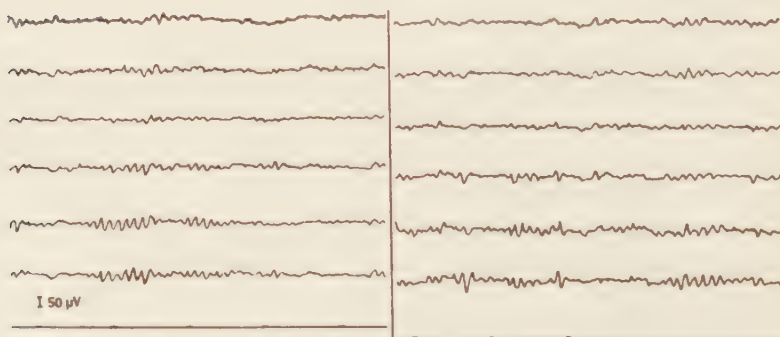
Fig. 3. Female twins, aged 42.
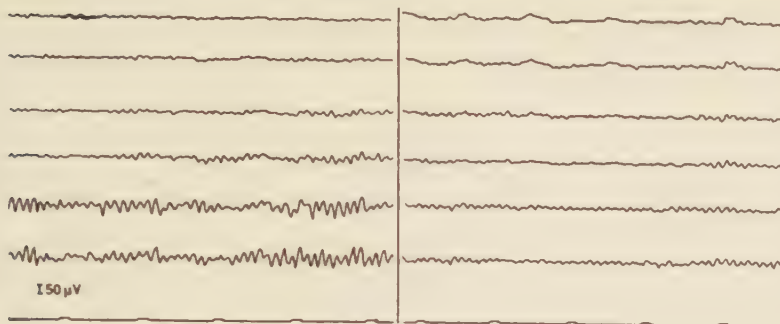
Fig. 4. Male twins, aged 46
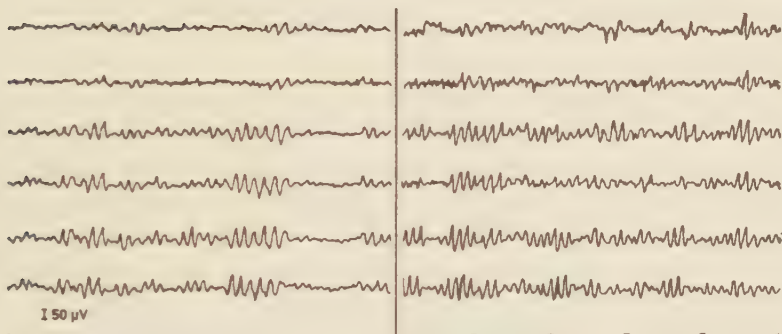
Fig. 5. Female twins, aged 49.
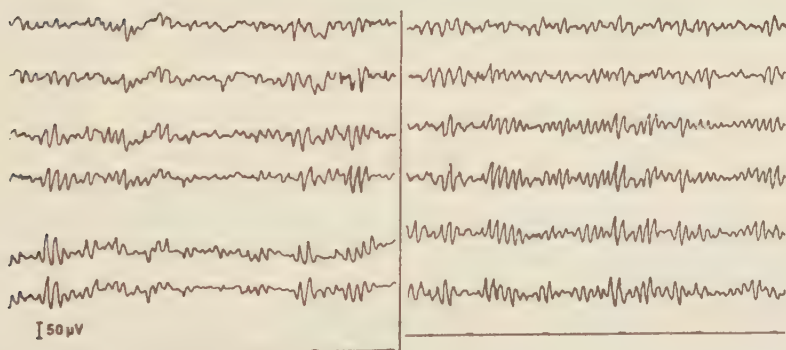
Fig. 6. Female twins, aged 56.
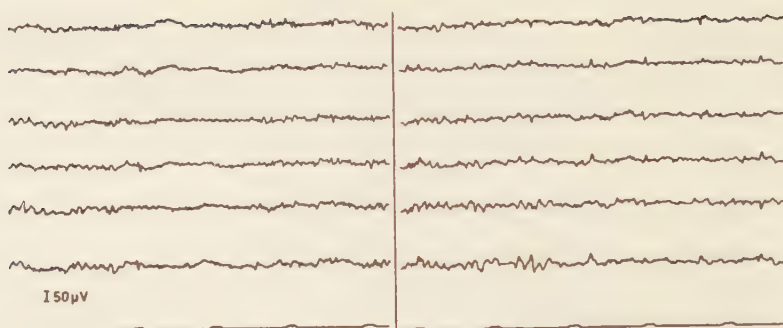
Fig. 7. Female twins, aged 71.
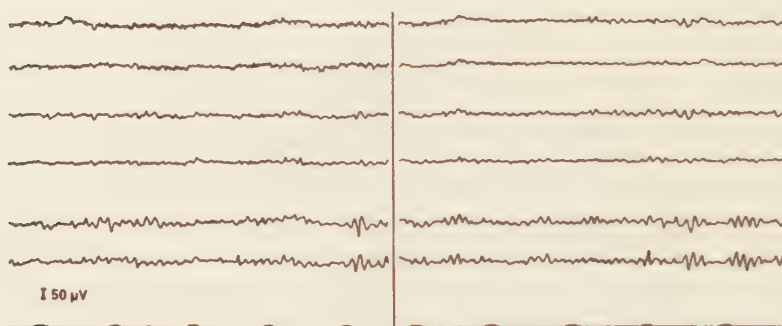
Fig. 8. Female twins, aged 72.

As appears both from the Table and from the Figures, very great similarity exists between the twin partners as regards the qualities registered. The frequency of the dominant activity is thus only significantly different in one pair (V). The amplitude of the dominant activity is, similarly, only different in one single pair (IV). The variations as regards the distribution in time of the dominant activity are somewhat greater; this may easily be explained from the very different distribution of the dominant activity in the same individual at different levels of consciousness. The reaction to hyperventilation and flicker was uniform in all the twin pairs investigated.

Where abnormalities are concerned, only one pair (II) presents slight discordance as one partner showed an isolated series of 6 per second activity frontally while the other had a completely normal EEG. As regards

the normal qualities, however, the EEG patterns in this pair were entirely identical. In two other pairs (I and VI) with EEG abnormalities, these occurred concordantly and were of completely the same nature in the two partners concerned.

It would naturally have been of particular interest if one of the uniovular twin pairs had shown marked discordance, as in such a case it becomes theoretically possible to discern the influences and differences in the external environment of the twins which could be considered responsible for the occurrence of the discordance. In this connection, we can only state that no such case was found in the present material. On the other hand, we had the opportunity of examining a pair of twin sisters aged 28 who had grown up apart and had only recently re-discovered one another. The EEG investigation showed entirely normal conditions in one twin while in the other a definite pathological curve was found with bilateral synchronous epileptic paroxysms. The twins themselves were of the opinion that they were uniovular but blood group examination demonstrated that this could not be the case.

In two of the pairs of twins, one of the twins (V_2 and VII_1) was ambidexterous and probably originally left-handed. No marked mirror imaging in the EEG was seen in either of the pairs but in V_1 the amplitude was slightly greater over the right than over the left hemisphere while the reserve was the case in V_2; in VII_1 the amplitude was equal over both hemispheres while in VII_2 it was greater over the right hemisphere.

The investigation thus demonstrates that uniovular twins who have grown up apart and thus have possibly been exposed to a series of differing environmental influences present EEG patterns which are practically uniform. These results confirm the findings of previous investigators and simultaneously, in our opinion, they may be interpreted as the conclusive and probably the only possible proof that the individual electroencephalographic pattern is determined predominantly by hereditary factors.

Summary

Eight pairs of uniovular twins between 22 and 72 years of age who had grown up apart from early childhood were investigated electroencephalographically. Practically complete concordance as regards both normal qualities and abnormalities was found. This is regarded as proof that the individual EEG pattern is primarily determined by hereditary factors.

Zusammenfassung

Acht eineiige Zwillingspaare im Alter von 22 bis zu 72 Jahren, die seit
früher Kindheit getrennt aufgewachsen waren, wurden elektroencephalo-
graphisch untersucht. Sie verhielten sich in bezug auf normale wie auf
abnorme Merkmale praktisch vollkommen konkordant. Das wird als Be-
weis dafür angesehen, daß das individuelle Hirnstrombild in erster Linie
durch Erbanlagen geformt ist.

Résumé

Des recherches électroencéphalographiques ont été faites chez 8 paires
de jumeaux univitellins âgés de 22 à 72 ans, qui depuis leur première en-
fance ont été élevés séparément. Le fait qu'on constate une concordance
complète au sujet des tracés normaux et abnormaux montre que l'électro-
encéphalogramme dépend en premier lieu de facteurs génétiques.

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HEMANGIOENDOTHELIOMA OF THE LIVER FOLLOWING INTRAVENOUS INJECTION OF THOROTRAST

By G. GRAMPA and A. TOMMASINI DEGNA

Thorotrast (Th.). first tested by *Radt* in 1930, was used extensively in the following years as a contrast medium in radiology, because of the rarity of its immediate damaging effects. Only some years after its use did experimental investigation and later observations on patients previously treated with Th. show the hazards resulting from its injection. Lesions due to Th. radioactivity have lately been described more frequently in view of the fact that time necessary for its manifestation has elapsed.

The most striking lesions induced by thorotrast are connective and epithelial malignant tumors which have been observed both in animal experimentation and in man, even though in some cases it be debatable whether the tumor is due to the presence of thorotrast.

Thorotrast-induced tumors have been reported most frequently in the liver where Th. is stored in a large amount. Inasmuch as primary malignant liver tumors, namely those of mesodermal origin, are rare, the frequent occurrence of such tumors in patients treated with Th. leads to the assumption that we are dealing with an oncogenic substance. The report of additional cases may be helpful for the solution of this problem. We therefore record a case of Th.-induced sarcoma of the liver, the first described in this country.

Case report

A. G., a 61 year-old white male, truck driver, was admitted to the Milan City General Hospital on March 27, 1956, with chief complaints of dyspepsia of three months duration,

jaundice and fever of eight days duration. Past history revealed that the patient was admitted to the same Hospital in 1932 and had received at that time three intravenous injections of Th. (25 cc. each) for investigation of an echinococcus cyst of the liver, which thereafter had been successfully operated upon.

Laboratory findings showed a moderate anemia (3.000.000 RBC. 74% Hb) and a change in the proportion of the protein fraction in the blood (Albumin 2,39; Globulin: total 5,65, alfa' 0,80, alfa'' 0,26, beta 0,60, gamma' 1,13, gamma'' 2,84). The serum bilirubin was 6,60 mg% (direct 2,82, indirect 3,64).

X-ray films showed numerous opaque nodules scattered in the liver and spleen and other opacities probably related to para-aortic and mesenteric lymph nodes.

The patient's physical conditions went progressively downhill and death occurred on April 11, 1956.

Final Clinical Diagnosis: Hepatic insufficiency (coma); liver cirrhosis; past history of cholecystitis, cholangitis and surgery for an echinococcus cyst of the liver.

Autopsy (n. 28303) *(excerpts):* The body was that of a fairly well nourished white man (weighing 73 kg.), whose estimated age was about 60. The skin and the external mucosae were deeply jaundiced. A well healed surgical scar about 18 cm. in length was present in the right side of the abdomen extending from the costal margin to the iliac region. The abdomen was distended, and, when opened, the peritoneal cavity contained an extimated 4000 cc. of a deep yellow cloudy fluid. Omentum, hepatic flexure of the transverse colon and gall bladder were packed together by means of massive adhesions to the inferior aspect of the liver and to the anterior abdominal wall, in the region of the above mentioned surgical scar. The liver was firmly adherent to the diaphragm extending 2 cm. below the costal margin. The splenic capsule was thick and fixed to the surrounding peritoneal surface. Slightly enlarged, whitish, firm lymph nodes were present at the hilum of the liver, mesentery, peripancreatic and para-aortal areas.

Liver: weight 1600 gr., size about normal. The external surface was nodular and distorted by irregular lobulation surrounded by furrows. The capsule was thickened and showed a white-greyish thread-like marking within the nodules. The cut surface revealed a fleshy brown tissue and an irregular lobulation caused by white thready lines similar to and continuous with those seen on the external surface. Some of the lobules were dry, mushy and necrotic in appearance. Round hemorrhagic nodules ranging from 0.2 to 2.5 cm. in diameter were scattered throughout the hepatic tissue (fig. 1). On the posterior surface of the liver there was a large irregularly shaped mass of hard connective tissue. On cross section this mass was composed of broad strands of white tissue merging into the surrounding liver parenchyma (fig. 2). The intrahepatic biliary ducts showed no significant changes. The gall-bladder had a thick opaque wall and contained a small amount of dark brownish viscid bile. The main branches of the hepatic artery, portal vein and hepatic veins revealed no pathological changes.

Spleen: weight 100 gr., size slightly reduced. The capsule was considerably thickened, the consistency rather hard. On cross section the red pulp was well retained. The connectival network was merely white, contrasting with the dark red color of the pulpa. The color of the connective strands resembled that of the thready lines seen in the liver. The lymphatic nodules were not recognizable.

Cross section of *lymph-nodes* showed the lymphatic parenchyma being replaced by the peculiar white firm tissue described in the liver and spleen.

Unfortunately no bone marrow was taken. Gross examination of the *other organs* showed no significant pathological changes besides the findings listed in the final diagnosis.
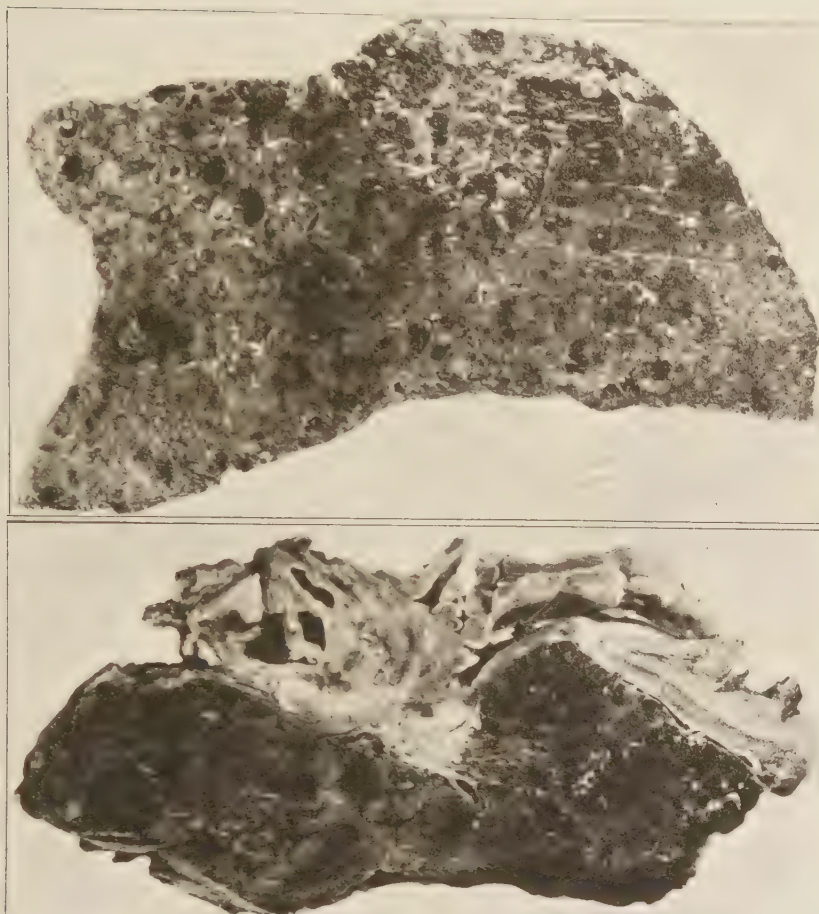
Fig. 1. Liver cut surface. Hemorrhagic and flashy nodules replacing the normal liver parenchyma. White naked eye visible depositions of thorotrast.

Fig. 2. Liver cut surface. Large hard mass in the posterior aspect of the liver made up of connective tissue with massive white thorotrast depositions.

Microscopic examination. Liver: the structure was deeply distorted due to the presence of conspicuous bands of fibrous connective tissue leading to an irregular lobular pattern. Within the lobules several highly cellular nodules were observed varying in shape and size, made up of neoplastic tissue, replacing and infiltrating the cords of liver cells (fig. 3). The nodules were composed of spindle cells arranged in interlacing whirls of twisted bands. Some nodules were mainly solid, others showed tiny clefts or wellformed vascular spaces with a trabecular structure (fig. 7) containing erytrocytes in the lumina. All the different stages from the solid to the angiomatous pattern (fig. 4) were recognizable. In the tumor tissue few remnants of liver parenchyma in the form of cellular cords or isolated cells were

Fig. 3 (left margin)

Fig. 5 (left margin)
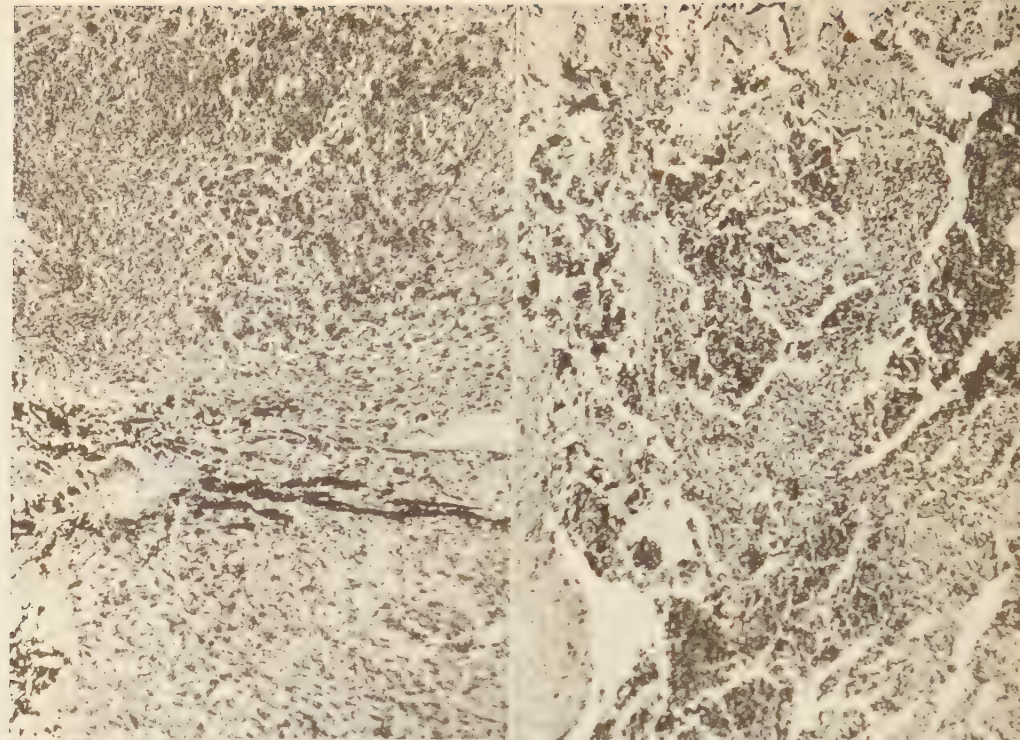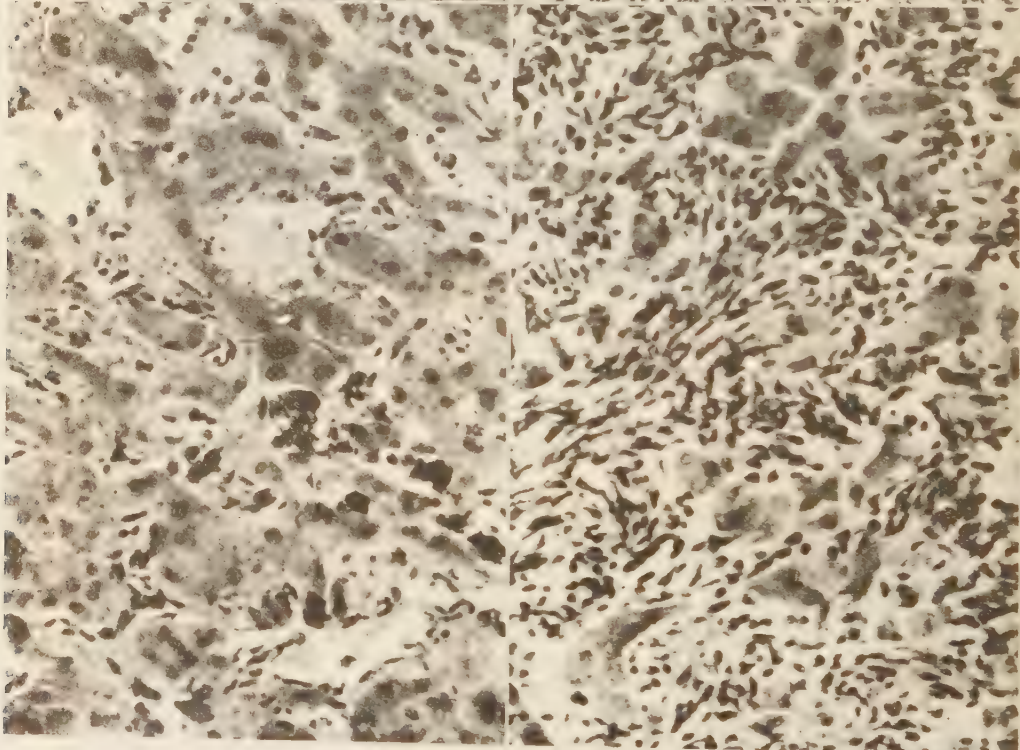
Fig. 3. Liver. A solid nodule of endotheliomatous cells. Thickening of the connectival interlobular septa with deposits of thorotrast. H.E. 45x.

Fig. 4. Liver. Neoplastic tissue showing an angiomatous structure. H.E. 50x.

Fig. 5. Liver. Hyperplasia of the Kupffer cells along dilated sinusoids. Thorotrast granules in the cytoplasms of fagocytes. H.E. 300x.

Fig. 6. Liver. Endotheliomatous tissue dissociating the liver parenchyma. Degenerative changes in the hepatic cells. H.E. 300x.
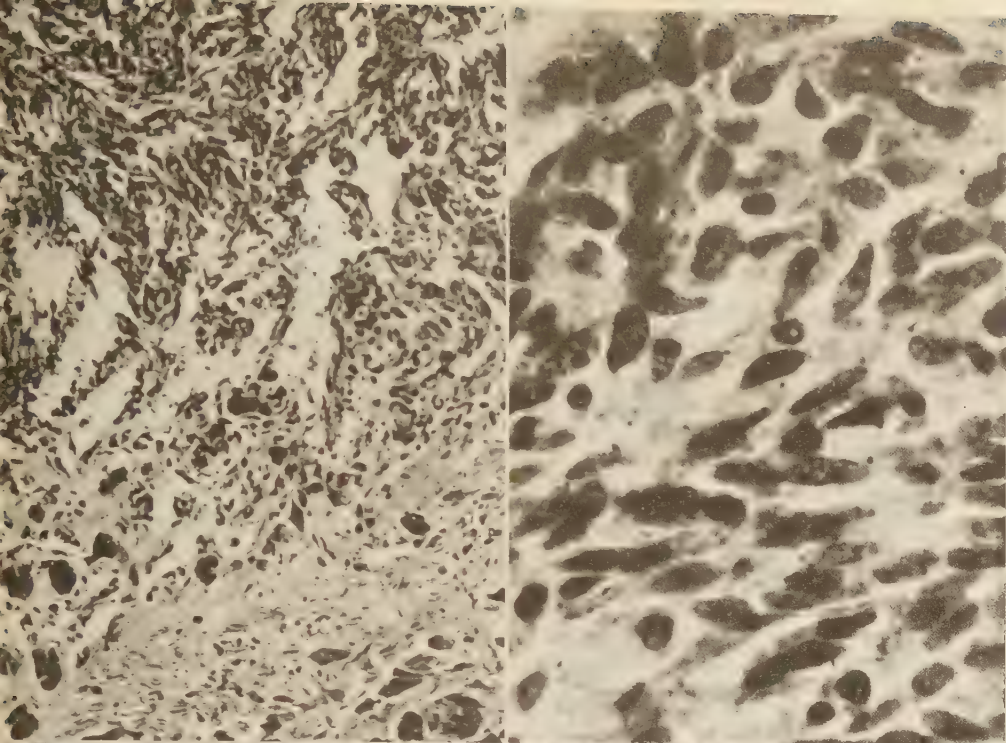
Fig. 8
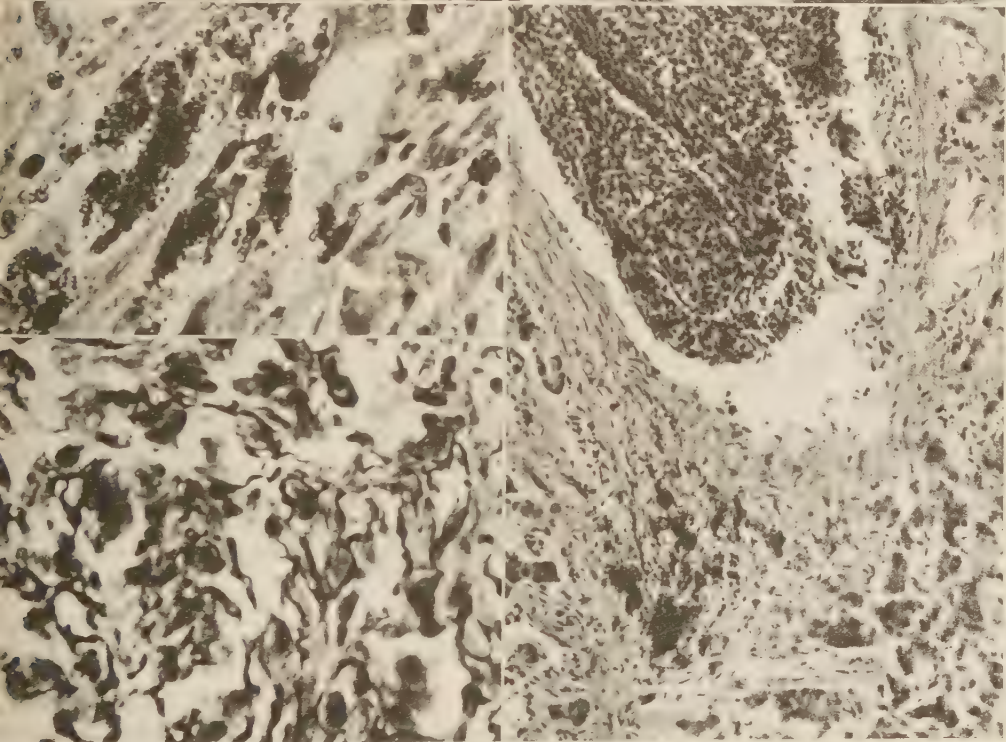
Fig. 11

Fig. 7. Liver. Irregular trabecular patterns of the neoplastic tissue. H.E. 190x.
Fig. 8. Liver. Mitotic figures within the endotheliomatous cells. H.E. 900x.
Fig. 9. Liver. Thorotrast granules, mostly intracellular, in a fibrous band. H.E. 550x.
Fig. 10. Liver. Silver-impregnated fibers in connection with the neoplastic cells. Gomori
reticulin stain. 820x.
Fig. 11. Liver. Island of tumor cells invading the lumen of a branch of the portal vein.
H.E. 120x.

observed. In some fields the lining cells of the sinusoids were very prominent, in others they formed continuous rows along the hepatic trabeculae the liver structure being essentially preserved (fig. 5), while in some areas the picture was that of liver trabeculae widely separated by multiple layers of tumor cells (fig. 6). The hemorrhagic nodules grossly described, showed a frankly cavernous pattern with large vascular spaces containing a large amount of blood separated by strands of connective tissue and lined by one or more layers of endothelial cells. In the contiguous tissues there were considerable hemorrhages. The remaining liver tissue showed fibrosis, degenerative changes and basophilic perivascular necrosis. The tumor cells were spindle-shaped with rather dense vesicular nuclei and a scanty basophilic cytoplasm. Some cells had hyperchromatic nuclei and focal mitotic activity was present (fig. 8). Plugs of tumor cells were seen within the lumina of branches of the portal vein (fig. 11). Some adenomatous proliferation was present arising from biliary ducts, while no nodular regeneration was noted in the hepatic cells. Thorotrast was recognizable as grey-brownish, refractile but not polarizing granules measuring 1–3 micra in diameter, which were deposited in large amounts in the portal spaces and in the subcapsular connective tissue, either loading the cytoplasm of macrophages or lying free within the fibers (fig. 9). Th. storage was also observed at the periphery of endothelial nodules and in the cytoplasm of tumor cells. Occasionally, findings suggesting Th. granules in the hepatic cells were present. However, because of the excessive cytoplasmic granulation, the nature of the cells cannot be definitely established. Silver stain showed a delicate network of reticulin fibers in the tumor tissue (fig. 10). Even in the solid nodules these fibers had a pattern resembling capillaries. At the boundaries of the endotheliomatous nodules, small foci of myeloid cells, including several plasma cells, were present (fig. 12). The walls of the blood vessels showed a moderate degree of fibrosis and focal areas of basophilic degeneration.

Spleen: Sections revealed extensive Th. deposition in the thickened fibrous trabeculae and capsule (fig. 13). The malpighian bodies were extremely atrophic; the red pulp was hyperplastic and very congested. In the cords and in the lumen of the sinuses, numerous Th. loaded macrophages and scattered myeloid cells (fig. 14) were seen. Hemorrhages were frequently observed in the remnants of the lymphatic tissue around the thickened centrofollicular arteries (fig. 13).

Lymph nodes: Sections of the macroscopically involved lymph nodes showed massive replacement of the lymphatic tissue by hyalinized fibrous bundles and deposition of grey-brownish Th. granules, laying either free in the tissue or in the cytoplasm of phagocytic cells.

As far as the identification of granules in the tissues is concerned, we feel that the history of thorotrast injections, the white chalky color of the grossly visible deposition in the liver, spleen and lymph nodes, and the morphology of the granules at microscopic examination allow a definite diagnosis. In our case further evidence for the identification of thorotrast was obtained from the following procedures:

1) Evidence of radioactivity by means of G. M. counter;
2) Histoautoradiographs of liver, spleen and lymph nodes revealed alpha tracts arising from the Th. granules (fig. 15).
3) X-ray diffraction patterns from tissue fragments showed the diffraction lines characteristic of thorium dioxide (fig. 16).

Final Anatomical Diagnosis: Hemangioendothelioma (Kupffer cell sarcoma) of the liver, fibrosis of the spleen and lymph nodes, with extensive thorotrast deposition.
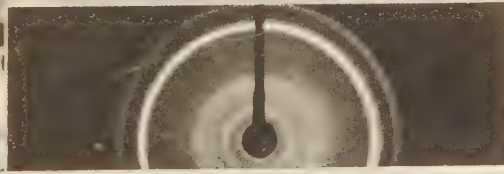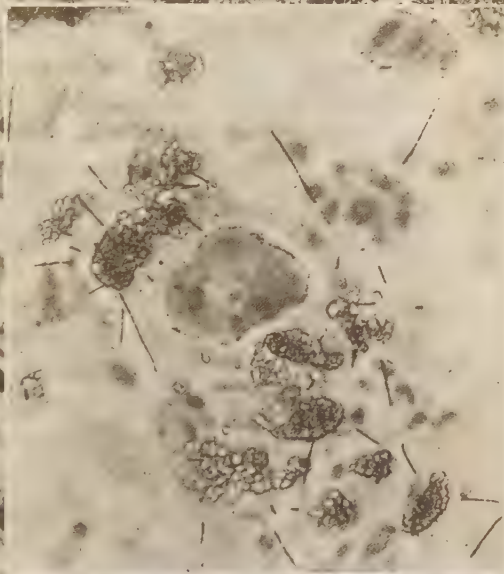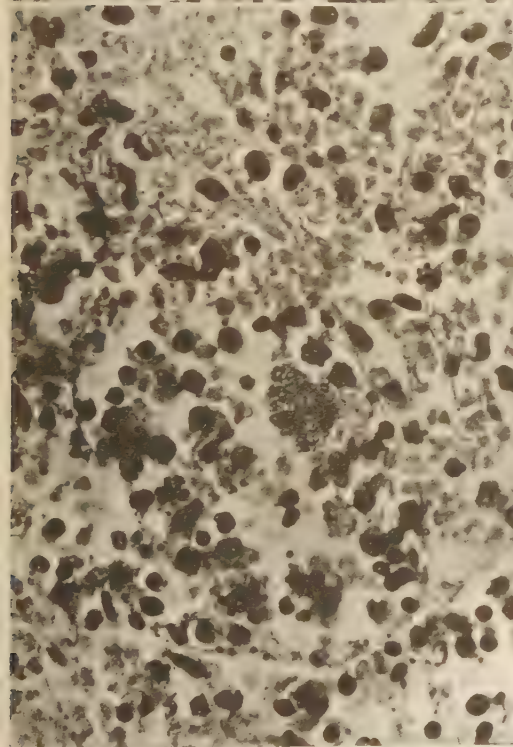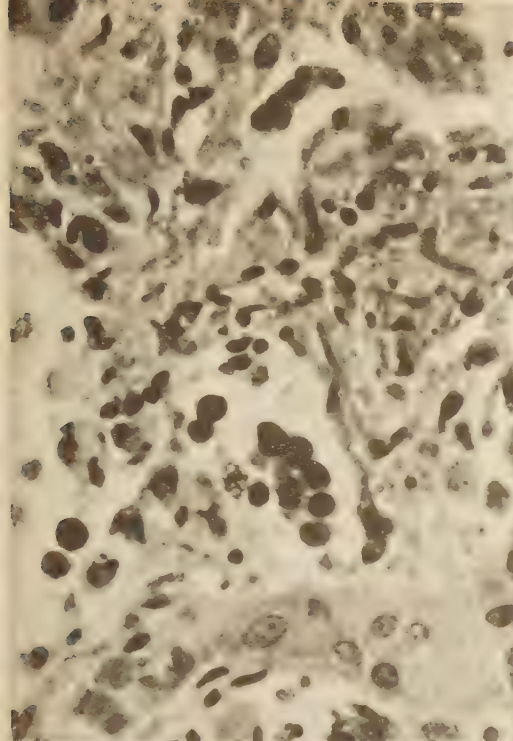
Fig. 13

Fig. 15

Fig. 16

Fig. 12. Liver. Focus of myeloid cells and thorotrast-laden histiocytes in the vascular spaces. H. E. 560x.
Fig. 13. Spleen. Large deposits of thorotrast in the thickened capsule and in hemorrhagic zones around the central follicular arteries. H. E. 22x.
Fig. 14. Spleen. Thorotrast-laden phagocytes and scattered myeloid cells in the congested sinuses. H. E. 550x.
Fig. 15. Liver histoautoradiograph. Alpha tracts arising from the thorotrast granules. 500x.
Fig. 16. X-ray diffraction pattern from a liver tissue fragment. The 1st, 2nd and 3rd lines have the reticular distances of 3,22 A°; 2,80 A°; 1,97 A°, due to the presence of thorium dioxide.

ascites, jaundice, dilatation of the right side of the heart, pulmonary congestion, mild edema of the brain, generalized arteriosclerosis, peritoneal fibrous adhesions in the upper abdominal quadrants, healed abdominal scar (history of surgery for echinococcus cyst of the liver).

Comment

Our case was a hemangioendothelioma of the liver in a 61 year-old man, who 24 years previously had received 75 cc. of thorotrast intravenously for diagnostic purposes. From the above description it is highly suggestive that the tumor originates from Kupffer's cells, therefore the term Kupffer cell sarcoma proposed by *Baker* and co-workers seems appropriate. Although no extrahepatic metastases were present, the tumor was considered malignant on the ground of its microscopic features, namely invasion of surrounding hepatic parenchyma, presence of tumor cells in the lumen of blood vessels and evidence of active proliferation as shown by mitotic figures. The foci of myeloid cells, which are reported in about 50% of liver endotheliomas, suggest an extramedullary hemopoiesis.

The tumor nodules were primarily located near the large Th. deposits in the connective strands of the liver and frequently Th. granules were observed in the cytoplasm of tumor cells. This association is very unlikely coincidental and it can be assumed that the liver neoplasm was caused by the Th. deposited in the organ since the time of injections. Due to the fact that Th. is stored in Kupffer's cells for an indefinite time, it may be assumed that the carcinogenic power of Th. affects Kupffer's cells, inasmuch as the long-lasting radioactivity of Th. is primarily related to alpha short-range radiations.

The instances of malignant tumors and leukemias in literature, which are possibly related to previous Th. administration, are reported in table I, which includes 40 cases and a personal observation. In several cases (n° 5, 10, 25, 28, 30, 31) the causal relationship between Th. administration and the growth of a tumor is not fully acceptable. Liver and biliary ducts account for 17 cases, of which three (n° 9, 36, 38) are non-specified tumors, two (n° 15, 37) a common duct carcinoma and one (n°23) a hepatic duct carcinoma. Of the remaining eleven cases, seven are hemangioendotheliomas (n° 2, 7, 13, 21, 22, 26, 35) and four are epithelial tumors (n° 16, 27, 29, 32).

The period of time elapsing between Th. administration and the appearance of a liver tumor ranges between 12 (*McMahon* and *Frühling's* cases) to 24 years (personal observation), exception is made for *Da Silva Horta's* first case, where the sarcoma developed 3 years after the injection of the

Table 1

Cases of malignant tumors and leukemias possibly related to Thorotrast administration

Author	Year	Sex	Age	Years of interval	Kind of administration and tumor
1) *Wohlwill*	1942	—	—	7	Hepatosplenography. Acute leukemia.
2) *MacMahon and others*	1947	f.	70	12	75 cc. intravenously. Endothelial cell sarcoma of the liver.
3) *Zollinger*	1949	m.	64	16	Pyelography. 30 cc. Spindle cell sarcoma of the kidney.
4) *Rudolphi*	1950	m.	51	34	Dacryocystography. Basal cell carcinoma of lower lid.
5) *Abrahamson and others*	1950	—	—	16	75 cc. intravenously. Bilateral alveolar carcinoma of the lung.
6) *Austoni*	1950	m.	47	12	Mammography. Carcinoma of the breast.
7) *Horta* (6)	1951	f.	—	3	Cerebral angiography. 20 cc. Endothelial cell sarcoma of the liver.
8) *Johansen and others*	1952	—	—	—	Dacryocystography. Carcinoma of the lacrimal duct.
9) *Johansen and others*	1952	—	—	—	Liver tumor (not specified).
10) *Vögtlin and others*	1952	—	—	18	Broncography. Squamous cell carcinoma of the bronchus.
11) *Johansen and others*	1952	—	—	—	Leukemia.
12) *Hofer*	1952	—	64	10	Maxillary sinus visualization. Squamous cell carcinoma.
13) *Lüdin*	1953	f.	63	14	Arteriography. 24 cc. Hemangio-endothelioma of the liver and spleen.
14) *Grebe*	1954	m.	51	7	Cerebral angiography. Myelogenous leukemia.
15) *Heitmann*	1954	m.	39	20	Hepatosplenography. Carcinoma of the bile ducts and liver.
16) *Matthes* (21)	1954	f.	54	21	80 cc. intravenously. Primary metastasizing carcinoma of the liver.
17) *Plenge*	1954	f.	54	6	Cerebral arteriography. Sarcoma at site of injection.
18) *Looney and others* (18)	1955	—	—	10	Hepatosplenography. 72 cc. Leukemia.
19) *Scheibe*	1955	—	—	17	Visualization of a fistulous tract of the cecum. 24 cc. Peritoneal malignant thorotrastoma.
20) *Gros*	1955	—	—	15	Maxillary sinuses visualization. Squamous cell carcinoma of the right m. s.

Author	Year	Sex	Age	Years of interval	Kind of administration and tumor
21) Tesluk	1955	m.	54	14	Cerebral angiography. Hemangioendothelioma of the liver.
22) Frühling	1955	—	—	12	Arteriography, hemangioendothelioma of the liver, spleen and bone marrow.
23) Roberts and others	1956	f.	45	17	Angiography. Carcinoma of the hepatic duct.
24) Budin and others	1956	f.	43	17	Mammography. Carcinoma of the breast.
25) Budin and others	1956	f.	65	16	Th. storage in the spleen. Carcinoma of splenic flexure of the colon.
26) Horta (7)	1956	m.	46	22	Aortography. Hemangioendothelioma of the liver.
27) Grossiord	1956	m.	51	21	Arteriography. Metastasizing cholangioma of the liver, cirrhosis.
28) Hackenthal	1956	m.	75	24	Purpose of injection not identified. Carcinoma of the bronchus.
29) Matthes (22)	1956	f.	52	23	Hepatosplenography. 60–70 cc. Cholangiocarcinoma.
30) Boemke	1956	m.	75		Purpose of injection not identified. Kidney carcinoma.
31) Federlin and others	1957	—	67	15	Hepatic carcinoma (primary ?).
32) Federlin and others	1957	m.	37	13	Cerebral angiography. Primary hepatic cell carcinoma.
33) Federlin and others	1957	f.	45	23	Salpingography. Carcinoma of the ovary.
34) Federlin and others	1957	f.	48	15	Cerebral angiography. Myelogenous leukemia.
35) Grampa and Tommasini	1958	m.	61	24	75 cc. hepatosplenography. Endothelial cell sarcoma of the liver.
36) Case quoted by Thomas					Liver tumor (non-specified).
37) Case quoted by Thomas					75 cc. intravenously. Carcinoma of the main bile duct.
38) Friedell, quoted by Looney (17)					Liver tumor (non-specified).
39) Squire, quoted by Thomas					Leukemia.
40) Hass and others quoted by Looney (17)					Leukemia.
41) Looney and others, quoted by Looney (17)					Leukemia.

substance. The long latency period for the induction of Th. tumors parallels the induction of cancers by other sources of radiation.

Hemangioendotheliomas represent about 50% of all the liver and biliary tract tumors, and 64% of liver tumors with specified histologic diagnosis. This is an incidence higher than the ratio between epithelial and connectival tumors of the liver in general.

Therefore hemangioendothelioma may be considered as the liver neoplasia electively induced by Thorotrast. We feel "thorotrast-liver-endothelioma" can be a proper term for a definite pathological entity, which most likely will include additional reports in the next few years and will remain isolated in the history of human tumors, since Th. has for a long time been almost completely rejected in medical practice. These induced tumors represent, however, an indication of the potential dangers resulting from the use of apparently harmless radioactive substances.

Summary

The authors report a case of hemangioendothelioma of the liver in a 61 year-old man who was treated with 75 cc. of thorotrast intravenously 24 years before death for diagnosis of an echinococcus cyst of the liver. Th. was stored in large amounts in the liver, spleen, mesenteric, peripancreatic, paraaortal and liver hilar lymph nodes. Spleen showed fibrosis, lymphatic atrophy and diffuse endotheliosis. Th. was demonstrated in the tissues by means of X-ray diffraction, histoautoradiographs and evidence of radioactivity on a G.M. counter. The histologic pattern of the hepatic tumor suggested an origin from the Kupffer cells of the sinusoids. Six other instances of liver hemangioendothelioma after Th. injection comparable with the personal observation were found in the literature. This is the tumor most frequently induced by Th. and the term "thorotrast-liver-endothelioma" is proposed for designating this definite pathological entity.

Zusammenfassung

Die Verfasser berichten über einen Fall von Hämangioendotheliom der Leber bei einem 61jährigen Manne, bei dem man 24 Jahre vor seinem Tode zur diagnostischen Darstellung einer Echinicoccus-Cyste in der Leber 75 cc Thorotrast i.v. injiziert hatte. Das Thorotrast war in großen Mengen in der Leber, der Milz und den mesenterialen, peripankreatischen und am Leberhilus gelegenen Lymphknoten gespeichert worden. Die Milz zeigte Fibrose, Atrophie des lymphatischen Gewebes und diffuse Endotheliose. In den Geweben wurde Th. durch Röntgenstrahlen-Brechung, Histo-

audioradiographie und Bestimmung der Radioaktivität mit Hilfe eines Geiger-Müller-Zählrohres nachgewiesen. Das histologische Bild des Leber-tumors legte einen Ursprung aus den Kupfferschen Sternzellen nahe. In der Literatur sind sechs andere, mit der hier vorgelegten Beobachtung ver-gleichbare Fälle von Hämangioendotheliom der Leber nach Th.-Injektion beschrieben. Da dieser Tumor der häufigste ist, der durch Th. induziert wird, wird die Bezeichnung «Thorotrast-Leberendotheliom» zur Benennung dieser gut definierten pathologischen Einheit vorgeschlagen.

Résumé

Les auteurs rapportent un cas d'hémangioendothéliome du foie chez un homme de 61 ans qui a été traité avec 75 cc de thorotraste intraveineux 24 ans avant sa mort, au fin de diagnostiquer un kyste échinococcique du foie. Le thorotraste se trouvait en grande quantité dans le foie, la rate, le mésenter, la région pancréatique, paraortale et dans les nodules lymphatiques hilaires du foie. La rate montrait une fibrose, une atrophie lymphatique et une endothéliose diffuse. Le thorotraste a été mis en évi-dence dans les tissus par la diffraction des Rayons X, des histoauto-radiographies et la mise en évidence de la radioactivité par le compteur de Geiger. L'image histologique de la tumeur hépatique déposait en faveur d'une origine au niveau des cellules de Kupffer. Dans la littérature, 6 autres cas d'hémangioendothéliome du foie après injection de thorotraste compa-rables à l'observation personnelle ont pu être trouvés. Celle-ci est la tumeur le plus fréquemment provoquée par le thorotraste et les auteurs proposent pour cette entité pathologique bien définie le terme de thorotraste-endo-théliome hépatique.

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STUDIES ON THE ERUPTION OF THE PERMANENT TEETH

IV. The effect upon the eruption of the permanent teeth of caries in the deciduous dentition, and of urbanisation.

By PETER ADLER

In areas where domestic waters contain more than 2 mg l of fluorides (parts pro million — ppm) eruption of the permanent teeth is somewhat retarded in comparison with those where the fluoride level is less than 0.5 ppm. No effect, however, is noticed in tooth eruption by fluoride levels of approximately 1 ppm although this latter concentration imparts to the teeth an almost optimal protection against caries *(Shortt)*. Contradictory findings were recorded, in a community with fluoride levels varying from 0.7 to 1.5 ppm in the single wells, in comparison with two adjacent communities with fluoride levels lower than 0.3 ppm, being due rather to an accelerated eruption of permanent premolars in the low fluoride areas, mainly in consequence of early extraction of deciduous molars in an increased number because of pulp involvement *(Adler[1])*.

Earlier eruption of permanent teeth in children brought up in towns than those living in a non-urbanised environment, is commonplace in most text-books of dentistry (cf. *Rebel*). This statement by *Röse* refers to a comparison of average tooth eruption ages of different teeth in boys and girls living in Dresden and in adjacent villages of Saxonia, and to a precedent paper by *Dietlein* (earlier eruption in girls from "better" than from "simpler" families in the same town).

In a previous study it was shown *(Adler[2])* that even the most incipient forms of urbanisation are associated with, and probably promote, higher prevalence of caries in the permanent as well as in the deciduous dentition. With these publications in mind, it seemed worth examining whether the earlier eruption of the permanent teeth in children brought up in towns is due to the heavier prevalence of caries in the deciduous dentition or to some other environmental factors that are simply summarised under the heading "urbanisation *per se*".

Material

This problem was studied in some communities living in the partly hilly and partly flat area in front of the Matra mountain in Hungary where the total population of the compulsory 8 class schools was dentally examined *(Adler[3,4])*. In two towns (*Eger* and *Gyöngyös*) low fluoride waters (fluoride level less than 0,3 ppm) are consumed from central supplies by more than 80% of the total population. In this study, these towns are regarded as *one* unit representing the "urbanised" population (U). Between them a viticultural area was found of 6 villages where prevalence of caries was high (although somewhat lower than in U). The school population of these villages forms the second unit of this study, and is thereafter labelled K. The town Hatvan and 9 adjacent villages in the near vicinity provided us with the third unit, with a partly urbanised and partly non-urbanised population having a markedly lower prevalence of caries mainly due to protection by moderately elevated fluoride levels of the domestic waters (P). Comparison of the permanent tooth eruption in these three areas is the main subject of the present paper.

It is surely of some advantage to have near adjacent areas for this study since some difference may exist as regards eruption of permanent teeth within the same country and between more distant geographical regions. In order to throw some light upon this problem —without being able to elucidate it sufficiently—, reference is made to an agricultural district in the Hungarian Alfoeld (Alf.) approximately 100 km from the nearest point of the afore mentioned areas, with 9 communities. For comparison's sake allusions are made to the revised tooth eruption data of *Gödény[1,2]*. The total number of examinees in the groups is: U=3735; K=1328; P=4165; Alf.=5648, while in *Gödény*s revised material 12 852 persons are collected. In all populations for both sexes 8 age groups (6½–13½ years of age) were formed, each group in the same population being approximately equal in number.

Methods

From the records of the visible teeth, tooth presence graphs were drawn up for each permanent and deciduous pair of teeth of the upper and lower jaw, for boys as well as for girls. From the graphs we determined:

(^{1}) average ages at the "shedding" of the deciduous teeth and at the eruption of the permanent teeth, with standard deviations;

(^{2}) the typical tooth formulae for "early", "average", and "late" eruptors at each full year of age, in agreement with *Fulton* and *Price*, *Gödény*[3] and *Adler*[5].

Nomogramms were constructed on a percentage basis for the presence of specified teeth at specified ages and relying upon these the sequence of areas was established according to the eruption of certain teeth.

Using the method of *Palmer*, *Klein*, and *Kramer*, the posteruptive tooth age was computed for several teeth, and comparisons were made between the populations relying upon the results obtained.

Finally, the mean number of deciduous, and permanent teeth was determined at specified ages in boys and in girls in U, K and P, and in Alf. with standard errors of the mean. As regards the data of *Gödény*, only mean values were available.

Table 1

Summarized data on dental caries in the three regions discussed and in one reference area

Region	Number of subjects 7–14 years of age	cer decid. molar index at the age of 8–9 years	CER-index at		
			age 8–9	age10–11	age 12–14
"P"	4165	211	42	84	117
"U"	3735	375	133	224	299
"K"	1328	316	85	162	223
"Alf."	5648	382	110	190	281

Age next birthday.
CER index: sum of carious, extracted and restored permanent teeth in 100 examinees.
cer decid. molar index: sum of carious, missing and not replaced, and filled deciduous molars in 100 examinees.

Caries data of U, K, P and Alf. are given in Table 1. Caries is assessed in tooth units (*Klein*, *Palmer*, and *Knutson*; *Adler*, *Bruszt*, and *Hradecky*—as regards permanent teeth; *Adler*[6]—as to caries of the deciduous molars). The data clearly demonstrate the marked difference between P on the one hand, and U, K, and Alf. on the other hand.

As regards the effect upon eruption of the successional teeth, the cer deciduous molar index deserves the most attention. In this respect, U and Alf. display a remarkable conformity, but values were not markedly lower in K.

Findings

1. *Average eruption ages* for boys and girls are given in Table 2. *In boys*, regarding the 11 data, earliest eruption is observed in 9 instances in U. In comparison with P, all teeth except the lower second molar erupt earlier in U than in P. Similarly, most teeth erupt in advance in U as compared to K. Four teeth erupt earlier in P, and 7 in K. – *In girls*, 7 teeth display the

Table 2. Average eruption ages, with standard deviations, in boys and girls in the three regions discussed and in the two reference groups (in years and months)

Tooth	Cödény	"P"	"U"	"K"	"Alf."
I. Boys		**Upper teeth**			
Central incisor	7:04.50 ± 0:11.9	7:05.50 ± 1:00.0	7:01.75 ± 0:10.6	7:02.00 ± 0:10.4	7:04.00 ± 0:11.9
Lateral incisor	8:07.00 ± 1:00.4	8:05.00 ± 1:00.2	8:01.00 ± 1:01.6	8:04.00 ± 0:11.1	8:05.00 ± 1:00.4
Cuspid	11:10.25 ± 1:05.4	11:08.75 ± 1:02.5	11:08.00 ± 1:03.2	11:10.00 ± 1:05.8	11:11.25 ± 1:06.9
First premolar	10:07.00 ± 1:08.9	10:05.25 ± 1:08.2	9:11.75 ± 1:07.1	10:06.00 ± 1:11.7	10:04.00 ± 1:08.4
Second premolar	11:05.50 ± 1:07.1	11:07.25 ± 1:05.6	11:01.50 ± 1:08.2	11:04.25 ± 1:08.2	11:04.75 ± 1:10.6
First molar					
Second molar	12:05.50 ± 1:02.8	12:02.50 ± 1:03.8	12:00.00 ± 1:04.3	12:04.25 ± 1:04.5	12:05.25 ± 1:03.4
		Lower teeth			
Central incisor					
Lateral incisor	7:09.00 ± 1:00.4	7:08.50 ± 1:00.2	7:05.50 ± 0:10.7	7:05.75 ± 0:10.7	7:06.75 ± 1:01.2
Cuspid	11:00.50 ± 1:03.2	11:01.00 ± 1:00.6	10:11.25 ± 1:03.8	10:09.25 ± 1:03.8	10:11.25 ± 1:06.2
First premolar	11:00.50 ± 1:05.1	11:02.00 ± 1:02.1	10:09.25 ± 1:06.7	10:11.75 ± 1:08.2	11:01.25 ± 1:06.5
Second premolar	11:10.00 ± 1:07.3	11:10.75 ± 1:04.8	11:07.75 ± 1:07.3	11:09.00 ± 1:07.3	11:10.75 ± 1:09.7
First molar					
Second molar	11:10.00 ± 1:03.6	11:08.25 ± 1:01.5	11:08.75 ± 1:02.3	11:10.50 ± 1:04.7	11:11.00 ± 1:05.4
II. Girls		**Upper teeth**			
Central incisor	7:01.25 ± 0:11.1	7:01.75 ± 1:01.3	6:11.00 ± 0:10.4	7:02.00 ± 0:11.5	6:11.75 ± 1:01.3
Lateral incisor	8:00.50 ± 0:09.5	7:11.50 ± 0:08.9	7:10.75 ± 0:08.8	7:11.50 ± 0:09.8	8:01.00 ± 0:11.7
Cuspid	11:02.50 ± 1:02.5	11:01.00 ± 1:05.2	10:11.50 ± 1:04.7	11:02.25 ± 1:03.2	11:02.50 ± 1:07.3
First premolar	10:03.00 ± 1:06.0	10:00.50 ± 1:05.8	9:10.50 ± 1:07.1	9:10.25 ± 1:06.9	10:00.75 ± 1:06.7
Second premolar	11:02.00 ± 1:06.5	11:00.50 ± 1:08.6	10:11.25 ± 1:05.6	10:08.50 ± 1:09.7	11:01.25 ± 1:09.1
First molar					
Second molar	11:11.50 ± 1:03.5	11:10.50 ± 1:04.5	11:10.50 ± 1:02.8	11:11.25 ± 1:01.3	12:02.25 ± 1:05.7
		Lower teeth			
Central incisor					
Lateral incisor	7:05.50 ± 1:00.0	7:06.50 ± 0:11.9	7:02.75 ± 1:00.8	7:03.00 ± 0:11.5	7:03.25 ± 1:01.0
Cuspid	10:01.50 ± 1:02.3	10:01.25 ± 1:03.2	10:00.00 ± 1:05.1	10:00.50 ± 1:03.6	10:01.00 ± 1:04.7
First premolar	10:05.25 ± 1:03.6	10:05.00 ± 1:04.5	10:03.25 ± 1:05.2	10:05.00 ± 1:04.3	10:04.50 ± 1:04.9
Second premolar	11:02.50 ± 1:08.3	11:03.00 ± 1:06.9	11:00.75 ± 1:07.1	11:06.25 ± 1:07.3	11:03.25 ± 1:07.3
First molar					
Second molar	11:04.00 ± 1:03.2	11:02.50 ± 1:03.2	11:03.50 ± 1:01.0	11:03.75 ± 1:03.6	11:06.75 ± 1:04.9

[1] earlier than demonstrable in our material.

Table 3. Average «shedding» ages, with standard deviations, in boys and girls in the three regions discussed and in the two reference groups (in years and months)

Tooth	Gödény	"P"	"U"	"K"	"Alf."
I. Boys					
Uppert teth					
Central incisor	7:03.00 ± 0:10.5	7:03.25 ± 1:00.4	7:00.00 ± 0:10.7	6:11.75 ± 1:08.5	7:01.50 ± 1:02.1
Lateral incisor	8:01.00 ± 1:01.3	7:11.00 ± 1:02.8	7:11.25 ± 1:00.2	7:08.25 ± 1:00.6	8:01.00 ± 1:02.5
Cuspid	11:06.50 ± 1:05.2	11:05.25 ± 1:03.4	11:04.25 ± 1:04.9	11:07.00 ± 1:07.1	11:07.50 ± 1:07.5
First molar	10:05.75 ± 1:10.1	10:02.00 ± 2:01.2	9:05.50 ± 2:02.9	9:05.25 ± 2:07.7	10:03.00 ± 1:11.4
Second molar	11:05.00 ± 1:10.9	11:04.25 ± 1:06.7	10:11.25 ± 2:00.8	11:02.25 ± 1:11.4	11:02.50 ± 1:10.4
Lower teeth					
Central incisor	1	1	1	1	1
Lateral incisor	7:07.00 ± 1:00.6	7:06.75 ± 0:11.5	7:02.50 ± 1:02.5	7:03.00 ± 0:09.1	7:04.50 ± 1:02.5
Cuspid	10:10.50 ± 1:03.4	11:00.25 ± 1:02.1	10:08.25 ± 1:04.9	10:05.25 ± 1:05.2	10:10.25 ± 1:07.6
First molar	10:11.25 ± 1:06.5	10:11.25 ± 1:08.6	10:04.00 ± 1:11.0	10:04.50 ± 1:07.8	10:10.75 ± 1:09.5
Second molar	11:06.50 ± 1:06.9	11:08.25 ± 1:04.8	11:03.50 ± 2:00.1	11:04.75 ± 2:00.3	11:08.25 ± 2:03.4
II. Girls					
Upper teth					
Central incisor	6:11.50 ± 1:00.0	7:00.00 ± 1:01.6	6:06.75 ± 1:01.0	6:11.00 ± 0:09.6	6:10.50 ± 0:11.5
Lateral incisor	7:09.00 ± 0:11.9	7:10.00 ± 0:11.9	7:05.50 ± 1:00.6	7:08.00 ± 0:11.7	7:09.25 ± 1:01.3
Cuspid	10:11.50 ± 1:04.9	10:09.50 ± 1:06.3	10:08.75 ± 1:05.1	10:07.50 ± 1:05.4	10:10.75 ± 1:07.8
First molar	10:02.00 ± 1:07.3	9:07.75 ± 1:08.0	9:06.50 ± 1:09.7	9:05.00 ± 1:08.4	9:10.75 ± 1:07.5
Second molar	11:01.25 ± 1:06.2	10:10.25 ± 1:09.5	10:10.00 ± 1:06.9	10:08.50 ± 2:00.1	11:00.50 ± 1:09.5
Lower teeth					
Central incisor	1	1	1	1	1
Lateral incisor	9:11.50 ± 1:03.4	9:11.75 ± 1:03.4	9:09.50 ± 1:03.9	9:11.25 ± 1:04.3	9:11.50 ± 1:04.1
Cuspid	7:03.50 ± 1:00.2	7:04.25 ± 1:01.9	6:11.00 ± 1:02.8	7:00.00 ± 0:09.3	7:01.50 ± 1:00.6
First molar	10:03.25 ± 1:04.5	10:02.25 ± 1:07.3	9:10.75 ± 1:09.9	10:00.25 ± 1:08.9	10:01.00 ± 1:07.6
Second molar	11:00.75 ± 1:03.8	10:11.50 ± 1:10.8	10:08.00 ± 2:10.1	10:10.00 ± 2:02.0	10:08.25 ± 1:07.1

¹ earlier than demonstrable in our material.

earliest mean eruption age in U. In comparing U with P, an earlier mean eruption age occurs in P in one instance only, and in another, identical eruption ages were stated, whereas all other teeth erupt earlier in U. Between U and K similar differences exist (9 teeth erupt earlier in U, two in K). In comparing P with K, earlier eruption occurs in P in 5 instances and in K in 4 instances, the mean eruption ages of 2 teeth being equal.

2. *The mean "shedding" ages* are summarized in Table 3. We are aware of the fact that our tooth presence data are unsuitable in determining a reliable average shedding age since all tooth presence curves are shifted towards the left by the "early" extraction of deciduous teeth. This is true as regards the teeth that are shed later and thus become carious in a greater number (dec. molars). Thus, in reality the average ages at the *loss* of the single pairs of deciduous teeth are given in Table 3 without taking into consideration whether spontaneous shedding occurred or the tooth was

Table 4

The typical tooth formulae of "late" eruptors (girls)

Age	Gödény	"P"	"U"	"K"	"Alf."
7	a b c d e – / a b c d e 6	a b c d e / a b c d e 6	a b c d e 6 / a b c d e 6	a b c d e / a b c d e 6	a b c d e / a b c d e 6
8	a b c d e 6 / 1 b c d e 6	a b c d e 6 / 1 b c d e 6	– b c d e 6 / 1 b c d e 6	a b c d e 6 / 1 b c d e 6	a b c d e 6 / 1 b c d e 6
9	1 b c d e 6 / 1 2 c d e 6	1 b c d e 6 / 1 2 c d e 6	1 – c d e 6 / 1 2 c d e 6	1 – c d e 6 / 1 2 c d e 6	1 b c d e 6 / 1 2 c d e 6
10	1 2 c d e 6 / 1 2 c d e 6	1 2 c d e 6 / 1 2 c d e 6	1 2 c d e 6 / 1 2 c d e 6	1 2 c d e 6 / 1 2 c d e 6	1 2 c d e 6 / 1 2 c d e 6
11	1 2 c d e 6 / 1 2 c d e 6	1 2 c d e 6 / 1 2 c d e 6	1 2 c d e 6 / 1 2 c d e 6	1 2 c d e 6 / 1 2 c d e 6	1 2 c d e 6 / 1 2 c d e 6
12	1 2 c d e 6 / 1 2 – d e 6	1 2 c – e 6 / 1 2 3 d e 6	1 2 c 4 e 6 / 1 2 3 d e 6	1 2 c 4 e 6 / 1 2 3 d e 6	1 2 c d e 6 / 1 2 3 d e 6
13	1 2 – 4 e 6 / 1 2 3 4 e 6	1 2 c 4 e 6 / 1 2 3 4 e 6	1 2 3 4 5 6 / 1 2 3 4 5 6	1 2 3 4 e 6 / 1 2 3 4 e 6	1 2 c 4 e 6 / 1 2 3 4 e 6
14	1 2 3 4 5 6 7 / 1 2 3 4 5 6 7	1 2 3 4 5 6 7 / 1 2 3 4 5 6 7	1 2 3 4 5 6 7 / 1 2 3 4 5 6 7	1 2 3 4 5 6 7 / 1 2 3 4 5 6 7	1 2 3 4 5 6 7 / 1 2 3 4 5 6 7

Permanent teeth are marked by 1, 2,...7, deciduous teeth by a, b,...e.

extracted in a lower or higher percentage of children before being spontane-
ously exfoliated. From the data, we see that *in boys*, the earliest shedding
occurred in 5 instances in U, and in 4 instances in K. Loss of a deciduous
tooth occured earlier in P than in U or K in one instance only. *In girls*,
6 teeth were shed earliest in U, and 3 in K. Not a single instance was ob-
served of an earlier average shedding age in P than in U or K.

The range of average eruption ages is generally smaller than of average
"shedding" ages. Comparing the 18 pairs of teeth, the reverse was ob-
served in 3 instances only (upper central incisor in boys, upper and lower
second dec. molars in girls); no difference was observed in the upper cuspid
of boys, while in all other instances the average "shedding" ages are
scattered over a broader range than are the average eruption ages.

3. As regards the typical tooth formulae—for example Table 4 shows
"late" eruptor girls—no gross differences were found between the five
regions. In some years, U is slightly in advance of the other populations,
and very few instances were found where another group apart from U was
in a more advanced stage of dentition. These irregularities are most often
seen among the "early" eruptors, but two instances are displayed e.g. also
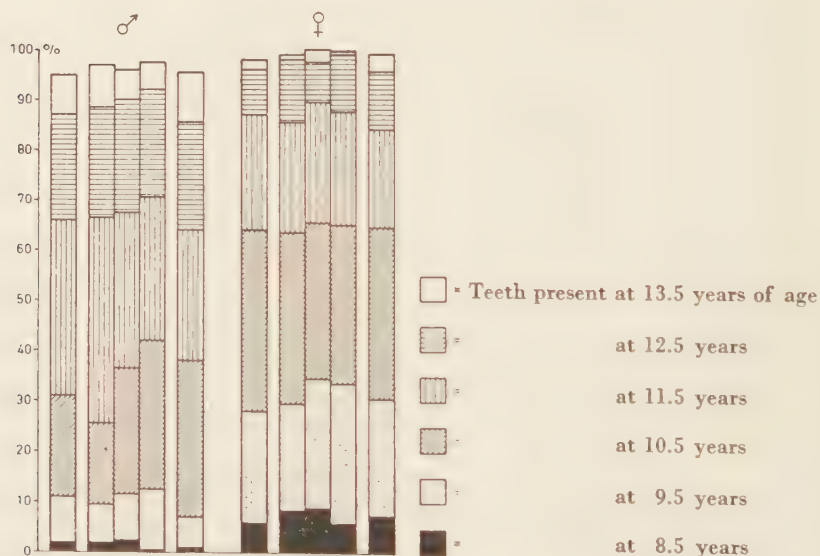
Fig. 1. Histogram showing the percentage of the lower cuspid present at specified ages.
Left half: boys, right half: girls. In both halves the column on the left relates to Gödény's
material, the right column to Alf. The three central columns depict conditions in P, U
and K respectively (from left to right).

Table 5

The sum of the sequence ratings of areas as regards the eruption of the cuspids, second molars, and all premolars within the range between 10 and 90%

Tooth	Gödény	"P"	"U"	"K"	"Alf."
Uper and lower canines	58,5	49,5	21,5	34,5	61
Upper and lower first and second premolars	130,5	112,5	51,5	96,5	134
Upper and lower second molars	46	24,5	33	48	58,5

Combined data for boys and girls.

by the "late" eruptor boys. In Table 4, for example, U is in advance of all other groups at the ages of 7 and 13, no differences being discernible between the five populations with 8, 10, 11 and 14 years. With 9 and 12 years, an equal stage is displayed in U and K, these being in advance of the other three regions.

4. From the nomograms of permanent tooth presence, the sequence of areas was established for the allegedly "normal" range of tooth eruption, the latter being determined in agreement with *Fulton* and *Price*, and *Gödény*[3] as between 10 and 90% instead of relying upon the double or treble standard deviation. In establishing the sequence of eruption of any particular tooth in the 5 areas, attention was paid to those ages only in which *at least in one* the 10th percentile of the particular tooth was attained, or the 90th percentile not surpassed. At all ages, the numerical value 1 was attributed to the area with the highest percentage of tooth presence, value 5 to the area with the lowest percentage and values 2, 3 and 4 were given to intermediates in descending order. Having covered the age range, the numerical values were added and some orientation was gained as to the standard of tooth eruption in the 5 populations. Results are shown in Table 5, and an example of nomograms in Fig. 1. In the premolars, summarily, there is a marked advance of U over all other groups, the second in the series being K. This also holds true for the canines. As regards second molars, the situation differs, the lowest sum being displayed by P, and followed by U; K and *Gödény*s group have approximately equal values and the series is completed with Alf. Alf. is the last group in tooth eruption of all teeth examined.

5. *Posteruptive tooth ages* were computed of all those for which we had average eruption ages and standard deviations. Arbitrarily, the age of 15 was chosen for comparisons. Results are shown in Table 6. The maximum

Table 6

Posteruptive tooth ages of the different teeth with 15 years of age,
and their sums in a few combinations

Tooth	Sex	Gödény	"P"	"U"	"K"	"Alf."
Upper central incisor	m	7:07.50	7:06.50	7:10.25	7:10.00	7:08.00
	f	7:11.75	7:11.25	8:01.00	7:10.00	8:00.75
Upper lateral incisor	m	6:05.00	6:07.00	6:08.00	6:08.00	6:07.00
	f	6:11.50	7:00.50	7:01.25	7:00.50	6:11.00
Lower lateral incisor	m	7:03.00	7:03.50	7:06.50	7:06.25	7:05.25
	f	7:06.50	7:05.50	7:09.75	7:09.00	7:08.75
Upper canine	m	3:02.37	3:03.17	3:03.54	3:01.40	2:10.57
	f	3:08.95	3:10.46	4:00.43	3:09.60	3:10.54
Lower canine	m	3:11.12	3:10.62	4:00.98	4:02.56	3:11.97
	f	4:10.63	4:11.28	4:11.85	4:11.28	4:10.45
Upper first premolar	m	4:04.29	4:04.55	5:01.12	4:06.60	4:07.10
	f	4:09.60	4:10.75	5:01.12	5:02.37	4:11.84
Lower first premolar	m	3:10.19	3:10.53	4:02.51	4:00.53	3:10.29
	f	4:06.60	4:06.45	4:08.76	4:07.42	4:07.77
Upper second premolar	m	3:07.11	3:06.54	4:02.68	4:00.51	3:07.19
	f	3:10.29	3:11.46	4:01.29	4:04.14	3:10.52
Lower second premolar	m	3:02.76	3:01.04	3:04.65	3:02.76	3:00.29
	f	3:08.76	3:08.21	3:11.78	3:06.55	3:08.46
Upper second molar	m	2:05.73	2:09.28	2:11.94	2:07.53	2:06.93
	f	2:11.71	3:02.02	3:01.03	3:01.25	2:09.83
Lower second molar	m	3:01.48	3:03.15	3:02.63	3:00.82	3:00.65
	f	3:08.09	3:09.61	3:08.20	3:07.69	3:06.61
All four upper incisors	m+f	57:11.50	58:02.50	59:05.00	58:09.00	58:05.50
All four lateral incisors	m+f	56:04.00	56:09.00	58:03.00	57:11.50	57:04.00
All four canines	m+f	31:06.14	31:11.06	32:09.60	32:01.68	31:03.06
All eight premolars	m+f	63:11.20	62:11.06	69:07.42	67:01.76	64:06.92
All four second molars	m+f	24:06.02	26:00.12	25:11.60	24:10.58	24:00.04
All 11 pairs of teeth whose average eruption ages were determined in Table 2	m	98:01.10	98:11.76	105:01.60	101:09.92	98:06.48
	f	109:04.76	110:06.96	113:04.92	111:07.60	110:01.04

posteruptive tooth age prevails in U in 15, in P and in K in 3–3 instances; in one instance the maximum is displayed by U and K contemporaneously. It is worth noting that maxima are displayed in P in all three instances by second molars. This is more conspicuously shown in the lower half of Table 6 where sums of posteruptive ages are given in different combinations. In incisors, canines and premolars, maximum values prevail in U, followed by K. The differences in the premolars are more marked. Since the post-eruptive ages of 8 premolars were summarized, and only of four teeth in all other types, the half difference observed in posteruptive premolar ages can only be taken into account. Between U and K this amounts to more than 14 months, whereas the difference of posteruptive canine ages is 7.92 months only. Similarly, between K and P, a half difference of more than 25 month is demonstrated in premolars whereas in the lateral incisors this amounts to 14.5 months only. – In the second molars, P is in advance of all other groups, confirming the results obtained with the sums of the sequence rates. – The advance of U over all other groups is most evident when totalling the posteruptive ages of all 11 pairs of teeth. Between the five populations, greater differences exist in boys than in girls. The maximum difference in girls (between U and *Gödény*s group) amounts to slighthly more than 4 years; in boys it surpasses 7 years. The difference between U and P amounts to approximately 74 months in boys, and to 34 months in girls. The advance of U in comparison with K is approximately 40 months in boys and 21 months in girls; thus, K is in advance of P by approximately 34 months in boys, and by 12–13 months in girls.

6. The average number of deciduous and permanent teeth at specified ages are summarized in Tables 7 and 8. From the beginning and continuing over the total age range (with a few exceptions only) the highest number of permanent teeth is found in U; and similarly, even though less regularly, the lowest number of deciduous teeth. – In comparing U, K and P, boys in all ages with the exception of 13½ years of age have more permanent teeth in U than in P. In girls even this single exception does not hold true. U is in advance of K with the exception of boys aged 9½, and girls of 9½ and 12½ years. K is ahead of P in boys up to 10½ years of age and in girls up to 9½ years, whereas in the older age groups of boys P seems to be ahead of K; in girls this holds true for the 10½ and 11½ year olds only. – With 7½, 8½ and 9½ years, boys in K have less deciduous teeth than their age mates in U; the reverse is seen in girls in whom the lower number was seen in K with 12½ years. In all other ages children in U have a lower number of deciduous teeth than their age mates in K. A more advanced stage of shedding prevails in all ages in U in comparison with P. Similarly,

K seems to be in advance of P in all ages, judging by the number of deciduous teeth.

Being primarily not interested in advanced eruption (and "shedding") of any sex or age but rather in the total trend of an advance of the urbanised area as compared to the non-urbanised one also suffering from dental caries, for statistical significance tests the data of both sexes and several ages were combined (Table 9). Since school can be entered only after the 6th birthday, the group of the 6½ year olds is not equally representative of the total population in all five areas; it thus seemed advisable to disregard the youngest group. As regards the eruption stage of the permanent teeth, a younger group (7½–10½ years) and an older group (11½–13½ years) was formed. Concerning the deciduous teeth, the total age range between 7½ and 11½ years was considered in one group. From the data of Table 9 it is obvious that in U and K the total number of deciduous teeth is signi-

Table 7

The average number of permanent teeth at specified ages

Age	Gödény	"P"	"U"	"K"	"Alf."
			Boys		
6½	4.46	4.53 ± 0.17	5.71 ± 0.23	4.70 ± 0.27	5.19 ± 0.18
7½	7.46	7.75 ± 0.21	8.52 ± 0.17	8.47 ± 0.30	7.95 ± 0.14
8½	10.48	10.82 ± 0.15	11.25 ± 0.16	11.08 ± 0.25	11.06 ± 0.17
9½	13.12	13.14 ± 0.15	13.45 ± 0.18	13.69 ± 0.28	12.98 ± 0.15
10½	15.50	15.28 ± 0.23	16.74 ± 0.27	16.15 ± 0.46	16.43 ± 0.18
11½	19.98	20.10 ± 0.28	20.40 ± 0.33	20.07 ± 0.58	19.66 ± 0.26
12½	23.83	24.48 ± 0.26	24.67 ± 0.23	24.00 ± 0.46	23.60 ± 0.25
13½	26.30	26.49 ± 0.18	26.48 ± 0.21	26.16 ± 0.29	26.04 ± 0.18
			Girls		
6½	5.45	5.21 ± 0.16	6.58 ± 0.23	5.69 ± 0.11	6.08 ± 0.17
7½	8.84	8.56 ± 0.18	9.21 ± 0.18	9.10 ± 0.32	8.94 ± 0.15
8½	11.66	11.43 ± 0.13	12.35 ± 0.16	12.03 ± 0.29	11.75 ± 0.19
9½	13.96	14.40 ± 0.20	14.86 ± 0.21	15.03 ± 0.39	14.32 ± 0.24
10½	17.83	18.34 ± 0.33	18.52 ± 0.29	18.31 ± 0.54	18.27 ± 0.32
11½	22.33	22.46 ± 0.35	22.87 ± 0.31	22.21 ± 0.49	21.77 ± 0.26
12½	25.41	25.72 ± 0.18	25.69 ± 0.21	25.86 ± 0.34	24.96 ± 0.20
13½	27.03	26.79 ± 0.16	27.86 ± 0.11	26.95 ± 0.22	26.63 ± 0.14

ficantly lower than in P and Alf. Neither between U and K, nor between P and Alf a significant difference exists. In comparing U and K with P this finding is not surprising if consideration is given to the heavier decay of the deciduous dentition in U and K. In spite of a markedly heavier prevalence of decay in Alf than in P (as regards the deciduous molars), there is no significant difference in the mean number of deciduous teeth. A difference nevertheless does exist amounting to 1.18 units e.g. in the $7\frac{1}{2}$–$9\frac{1}{2}$ year olds; in the two youngest years, a difference of 1.54 units is demonstrable. In these two years, the cer deciduous molar index is greater in Alf by 171 per 100 persons than in P. This fairly agrees with the difference in the number of deciduous teeth.

As regards the mean number of permanent teeth, the younger age group in U is significantly in advance as compared to P and Alf, but not significantly in advance in comparison with K although an advance is

Table 8

The average number of deciduous teeth at specified ages

Age	Gödény	"P"	"U"	"K"	"Alf."
			Boys		
$6\frac{1}{2}$	17.93	17.55 ± 0.15	16.35 ± 0.24	17.71 ± 0.27	16.92 ± 0.17
$7\frac{1}{2}$	15.05	14.83 ± 0.22	13.67 ± 0.19	12.95 ± 0.32	14.35 ± 0.14
$8\frac{1}{2}$	12.48	11.61 ± 0.17	11.20 ± 0.17	11.03 ± 0.24	11.59 ± 0.14
$9\frac{1}{2}$	10.19	9.87 ± 0.16	9.15 ± 0.18	9.06 ± 0.33	10.11 ± 0.15
$10\frac{1}{2}$	8.06	8.17 ± 0.20	6.57 ± 0.24	6.71 ± 0.34	7.50 ± 0.19
$11\frac{1}{2}$	4.73	4.70 ± 0.25	4.19 ± 0.25	4.51 ± 0.45	4.95 ± 0.22
$12\frac{1}{2}$	2.31	1.95 ± 0.19	1.63 ± 0.19	1.91 ± 0.31	2.48 ± 0.17
$13\frac{1}{2}$	0.91	0.69 ± 0.11	0.65 ± 0.13	0.67 ± 0.12	1.12 ± 0.13
			Girls		
$6\frac{1}{2}$	17.32	17.15 ± 0.16	15.65 ± 0.24	16.54 ± 0.37	16.34 ± 0.17
$7\frac{1}{2}$	14.17	14.20 ± 0.20	12.84 ± 0.20	13.24 ± 0.33	13.77 ± 0.14
$8\frac{1}{2}$	11.62	11.69 ± 0.18	10.21 ± 0.19	10.70 ± 0.27	11.18 ± 0.15
$9\frac{1}{2}$	9.48	8.83 ± 0.20	7.95 ± 0.20	8.09 ± 0.36	8.85 ± 0.19
$10\frac{1}{2}$	6.30	5.65 ± 0.28	5.28 ± 0.23	5.21 ± 0.44	5.55 ± 0.20
$11\frac{1}{2}$	3.19	3.07 ± 0.25	2.44 ± 0.21	2.88 ± 0.34	3.29 ± 0.19
$12\frac{1}{2}$	1.26	1.21 ± 0.12	0.96 ± 0.13	0.77 ± 0.18	1.52 ± 0.14
$13\frac{1}{2}$	0.44	0.65 ± 0.11	0.22 ± 0.05	0.40 ± 0.13	0.40 ± 0.09

Table 9

Summarized tooth presence data in certain age groups
and the statistical significance of differences
Combined data of both sexes

Tooth type and age group	Gödény	"P"	"U"	"K"	"Alf."
Deciduous					
7½–11½	95.27	92.62 ± 0.68	83.48 ± 0.66	84.38 ± 1.10	91.14 ± 0.55
Permanent					
7½–10½	98.85	99.72 ± 0.58	104.90 ± 0.59	103.86 ± 1.04	101.70 ± 0.57
11½–13½	144.88	146.04 ± 0.60	147.97 ± 0.60	145.25 ± 1.02	142.66 ± 0.54

Groups compared	Decidous teeth	Permanent teeth	
	7½–11½	7½–10½	11½–13½
"P" versus "U"	9.14 ± 0.94[2]	−5.18 ± 0.83[2]	−1.93 ± 0.85[1]
"P" versus "K"	8.24 ± 1.29[2]	−4.14 ± 1.18[2]	0.79 ± 1.18
"P" versus "Alf."	1.48 ± 0.87	−1.98 ± 0.81[1]	3.38 ± 0.81[2]
"U" versus "K"	−0.90 ± 1.29	1.04 ± 1.19	2.72 ± 1.18[1]
"U" versus "Alf."	−7.66 ± 0.86[2]	3.20 ± 0.82[2]	5.31 ± 0.81[2]
"K" versus "Alf."	−6.76 ± 1.23[2]	2.16 ± 1.18	2.59 ± 1.15[1]

[1] The difference is probable (greater than its double standard error, but less than 2.5 times the standard error).

[2] The difference is statistically significant (greater than its treble standard error).

demonstrated. That K is ahead of P is statistically significant too, whereas no significance can be attributed to differences between U and K, and between K and Alf. In the older age group, a significant difference was found between U and Alf, between P and Alf, with a more advanced stage in U and P respectively. The differences between U and P, and between U and K are statistically probable (with a more advanced stage in U).

Discussion

According to our findings, urbanisation seems to exert an accelerating influence upon the eruption of the permanent teeth, besides the accelerating effect of the heavy decay of the deciduous dentition and consecutive "early" extractions that are connected in some way with urbanisation.

Urbanisation seems capable of compensating to some degree the accelerating influence of "early" extractions, at least according to our findings, as less difference was found in some instances between our partly urbanised and caries-protected group and our group K, than between the latter and U. How far the markedly advanced eruptional stage in U is influenced by urbanisation and by caries (and extractions) of the deciduous dentition—as compared to P—cannot be stated in a reliable manner. Apparently, an additional effect of urbanisation and early extractions is noticed in these cases.

The accelerating effect of urbanisation was first stated by *Röse*, and later confirmed in a thorough study by *Ekman*. Their findings are fully corroborated by ours. Similar differences were shown to exist as regards tooth eruption between the different socio-economic classes. Generally a more advanced eruptional stage was demonstrated in well-to-do children than in poor children *(Dietlein, Röse)*. *Hellman*s findings are partly contradictory, as he showed later eruption of premolars in "wealthy" and not in "poor" children. A satisfactory explanation was given by *Leslie* who demonstrated the accelerating or retarding influence of extraction of deciduous molars dependent on the time of the extractions.

In explaining the accelerating effect of urbanisation on tooth eruption, consideration must be paid to the accelerated general development of urbanised children in comparison with inhabitants of rural areas. Similar differences seem to exist between children from the various socio-economic conditions. According to *Röse* some importance was attributed to the supposedly purer racial stock of families in the higher socio-economic levels. The well known fact that girls are in advance of boys as regards eruption of the permanent teeth, leads to the assumption that this process is influenced by sexual maturation that occurs markedly earlier in girls than in boys. This item is emphasized by *Röse* as well as by *Dietlein*. Recently it was shown that a good correlation exists between areolar development of mammae and tooth emergence in girls *(Ápostolides-Talmers)*. In girls menarche is a conspicuous sign of sexual maturation. It is multitudinously proven (cf. *Bennholdt-Thomsen*) that menarche occurs earlier in towns than in rural areas; it depends, however, according to the *Kinsey*-report also on the educational level. The difference between the highest and lowest educational level amounts to 5–6 months as regards menarche. This difference is more marked than that prevailing between the average tooth eruption ages of our different groups in Table 2. Taking into consideration the differences in the totals of the posteruptive tooth ages, still greater differences were stated, however, between our five population groups. In

boys there is no similar conspicuous sign of sexual maturation that could be relied upon.

According to *Portmann* the shedding of deciduous teeth and their replacement by permanent successors starts when the brain has attained approximately 90% of its total mass, this statement being valid *grosso modo* in apes, anthropoids, as well as in man. Urbanisation effects, according to *Bennholdt-Thomsen*, are due to an increased vegetative, incretoric and cerebral reactivity of a certain part of the total population within a country that prefers townlife. Completing these ideas, one may suppose that urbanisation exerts a promoting influence upon the development of the brain, and this also induces secondarily, together with other somatic symptoms, the accelerated tooth eruption. Seemingly contradictory findings were recorded by *Cattell* who showed that the average number of teeth in superior, unselected and feeble-minded boys comes unexpectedly near to coinciding with one another. On the other hand, *Orsós* and *Bartha* showed experimentally in the rat that a change in the eruption rate of the incisor can be induced by pharmaca acting primarily upon the central nervous system.

Summary

It was shown that urbanisation exerts an accelerating influence upon eruption of permanent teeth that is not dependent on the "early" extractions of their deciduous predecessors due to caries. The latter item also exerts an accelerating influence, at least under conditions prevailing in Hungary at the time of these investigations (most extractions of deciduous teeth are performed after the 7th birthday). These statements are made according to an analysis of the tooth presence data in an urbanised region (U), in a non-urbanised one in its vicinity with equally heavy decay in the deciduous molars (K), and in a moderately fluoride-protected area (P). Comparisons are also made with data collected by *Gödény* and tooth presence data from a district of the Hungarian *Alfoeld*. Average "shedding" and eruption ages were stated for the different teeth, tooth formulae were studied of early, average and late eruptors, sequence ranges of tooth eruption were computed, and total posteruptive tooth ages with 15 years of age were determined. The average number of deciduous and permanent teeth present in the mouth at specified ages were also studied.

Zusammenfassung

Es wurde gezeigt, daß die Urbanisation den Durchbruch der bleibenden Zähne beschleunigt, unabhängig von dem höheren Kariesbefall des Milch-

gebisses und von den hierdurch bedingten frühzeitigen Milchzahnextraktionen. Auch die Letzterwähnten wirken beschleunigend auf den Zahndurchbruch, zumindest unter den in Ungarn zurzeit obwaltenden Verhältnissen (die meisten Milchmolarenextraktionen erfolgen nach dem 7. Geburtstag). Diese Feststellungen beruhen auf den Zahnpräsenzdaten einer urbanisierten Gruppe (U), einer nicht-urbanisierten, in nächster Nachbarschaft wohnenden, von der Milchzahnkaries praktisch gleich stark befallenen Gruppe (K) und einer durch F mäßig karies-geschützten Gruppe (P). Zu Vergleichszwecken wurden die Zahnpräsenzdaten von *Gödény* und eines Bezirkes aus der ungarischen Tiefebene herangezogen. Es wurden das Durchschnittsalter beim Verlust der einzelnen Milch- und beim Durchbruch der einzelnen bleibenden Zähne, die typischen Zahnformeln von «früh», «durchschnittlich» und «spät» zahnenden Kindern, die Eruptionsfolge der einzelnen Gebiete, das posteruptive Zahnalter, die durchschnittliche Zahl der Milch- bzw. bleibenden Zähne zu verschiedenen Lebensjahren bestimmt.

Résumé

Il a été possible de démontrer que le fait d'habiter dans une ville exerce une influence accélératrice sur l'éruption des dents permanentes et ceci indépendamment du fait de l'extraction prématurée des dents de lait nécessitée par la carie. Cette dernière a d'ailleurs également une influence accélératrice, tout au moins dans les conditions existant en Hongrie au moment de ces investigations (le plus souvent l'extraction des dents de lait a été faite avant l'âge de 7 ans). Ces conclusions sont basées sur une statistique concernant le nombre de dents présentes chez un groupe habitant la ville (U), chez un autre groupe atteint d'une façon semblable de caries, mais habitant les faubourgs (K) et d'un troisième groupe protégé partiellement par le fluor (P).

A titre de comparaison, une statistique de *Gödény* et une autre provenant de la plaine hongroise ont été prises en considération. L'âge moyen de la perte des différentes dents de lait et l'apparition des différentes dents définitives, les formules typiques pour les enfants ayant une éruption précoce moyenne ou tardive, ainsi que les étapes consécutives de l'éruption des différents groupes de dents ont été établis. Finalement le nombre des dents des 1re et 2e dentitions présentes au même moment a été fixé pour chaque groupe d'âge.

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J. V. NEEL, W. J. SCHULL and co-workers: The Effect of Exposure to the Atomic Bombs on Pregnancy Termination in Hiroshima and Nagasaki. Nat. Ac. Sc.–Nat. Res. Council, Washington 1956. Price: $ 2.00, pp. 241.

The book has 15 authors, but both the style (which has been held uniform) and the easily surveyed paragraphing of the chapters correspond closely to the form in the well known textbook by the two principal authors.

During the years 1948–54, information was collected in Hiroshima and Nagasaki on almost all the pregnancies which had proceeded beyond the 5th foetal month, in all 76,626, where in approximately one half of the cases one or both the parents had been irradiated during the atom bomb attacks, approximately $2/3$ with dosages of a few r and only in less than 1% of the cases with doses exceeding 100 r. The pregnancies were investigated with reference to the sex ratio of the offspring, the frequency of malformations and stillbirths, the neonatal mortality, the weight at birth and, in the case of $1/3$ of the offspring, the mortality during the first nine months of life and some few body measurements at an age of nine months. The results are set out in 147 tables and 29 figures, and are subjected to a comprehensive statistical treatment by means of χ^2-tests and variance analysis, whereby it has been impossible to demonstrate significant differences between the offspring of irradiated and non-irradiated persons or of irradiated persons who had small and large radiation doses. In some quite few cases a significant effect of the irradiation of the parents is suggested, but these cases cannot be taken as any proof, as on the statistical theory some positive tests must be anticipated among so many analyses as are here carried out.

However, the figures presented permit the conclusion that in the case of the irradiated persons the mutation rate/r can have been 6 × greater than that found for Drosophila, and that the „doubling dose" cannot have been as small as 10 r. The book concludes with a valuable discussion on the general problems of radiation genetics, first and foremost on the lines previously laid down by MULLER.

The explanation of the statistical procedures can only be appreciated by specialists in that field, but the presentation in the many tables and the conclusion drawn are easily understood with the help of modest statistical knowledge.

NEEL ans SCHULL's book must remain a major work for all those wishing to engage in studies on the effect of radiation on human heredity, it demonstrates the difficulty of this field of research and how slight the probability of reaching certain results is, but at the same time it is a challenge to take up new topics for investigation.

B. ZACHAU-CHRISTIANSEN

Effect of Radiation on Human Heredity. WHO, Geneva 1957. Price: £ 1, $ 4.00, Sw. fr. 12.—, pp. 168.

In direct association with the 1st International Congress of Human Genetics, a Study Group on the above subject, convened by WHO, was held in Copenhagen from 7 to 10 August, 1956. The group consisted of 26 scientists and doctors, almost from the West. A report on the work of this group is now available.

The book is divided into two sections, the first section being the report itself. In this, the importance is stressed of control of both the medical and technical use of ionizing radiations, as an effective control in itself operates to cut down the amount of radiation involved, of whose possible danger to man the group is not in doubt. Opinions are then passed on the question of research problems: no clear directives are laid down for further research, but a series of topics are recommended, whereby practically speaking the entire field of genetics in its widest conception is included in the scope of radiation genetics research. The group recommends the training of more geneticists and the establishment of more genetic institutions, with which scientists from other disciplines together with statisticians should also be associated. A registration of hereditary diseases is necessary to the same extent as, for instance, with epidemic diseases, and it should be possible for a U.N. Agency to provide advice and recommendations for research on request.

The major portion of the book, part 2, comprises the contributions presented by 12 of the members at the meeting of the group. A series of problems on the effect of radiation on human heredity and allied topics are discussed in small articles of about 10 pages. Although in the first instance the book is only of interest for those geneticists wishing to learn what the WHO Study Group concerned itself with, the articles can be interesting for others, for even though the contents can be found in up to date textbooks, in the reports of the Med. Res. Council, G.B. and the Nat. Acad. Sc., U.S.A. on radiation hazards, and in current periodicals, a number of the articles represent brief surveys of value by specialists in the respective fields.

MULLER discusses the laws found for point mutations induced by radiation, PENROSE, STEVENSON and NEEL deal with methods for the estimation of spontaneous mutation rates and the difficulties and sources of error in these estimates. PENROSE mentions in addition the possibility that phenocopies are somatic mutations, STEVENSON points out particularly how very few new mutants will be found in populations of the order of millions after 100% increase in the background radiation, and NEEL goes into the particularly important problem, that irradiation leads to a greater frequency of deleterious mutations

than visibles (visibles:lethals:semilethals + deleterious mutations = 1:4:16 − 1:6:30). T. C. CARTER and BRUCE WALLACE submit certain theoretically based considerations on the nature of the mutant genes induced by ionizing radiation.

As lines for future research, LEJEUNE mentions the use of sex ratio determinations as a measure for detecting radiation-induced mutations in the first generation (X-linked lethal mutations), GOPAL-AYENGAR recommends genetic studies of high population densities in regions with high background radiation, as in the monazite areas along the coastline of India, and FREIRE-MAIA mentions that there are regions in Brazil with high levels of inbreeding, and investigations here would be valuable for determining the frequency of recessive genes. Finally, NEWCOMBE shows how the Canadian genetic register should be built up so as to allow trends in hereditary disease to be followed.

In an excellent article, based partly on his own investigations, SIEVERT discusses the quantity of radiation to which we are exposed, particularly from natural sources of radiation, and provides a number of rules covering the variation in the background radiation. COURT BROWN, in a short article, discusses how much of the annual gonad dose to the population is contributed by diagnostic radiology and therapeutic radiology, estimates being respectively 10–58% and about 8% of the background radiation.

B. ZACHAU-CHRISTIANSEN.

C. H. Waddington: **The Strategy of the Genes.** George Allen and Unwin Ltd. London 1958. IX + 262 p. 28 sh.

This little book comprises five essays dealing with two of the most fundamental problems of the theoretical biology – firstly, the nature of biological organisation and the developmental processes, which bring it into being, and secondly, the theory of evolution. In discussing the first of these problems professor *Waddington* utilizes his immense knowledge of both embryology and genetics and succeeds in propounding an excellent hypothesis on the nature of those biological processes, which result in living things having definite and characteristic structures. The understanding of this theoretical discussion is facilitated through the demonstration of the author's favorite model of gene action, his "epigenetic landscape", in which the characters during development have to follow the clefts and valleys, symbolizing the developmental "canalisation" of different characters.

On this model, too, the discussion of evolution is based, and professor *Waddington* demonstrates how a synthesis of population genetics and his developmental ideas provides a more penetrating insight in the question, how evolution brings into existence organisms so well adapted to the requirements of their life. May the evolutionary processes be explained merely as a result of random mutation and selection – the modern genetical theory in evolution – or is it possible that environmentally-induced mutations some way or other may be adaptive? This is the ancient controversy about "the inheritance of aquired characters", and the author suggests that this question has not been satisfactorily settled as yet. In reality, in his developmental model he finds a way of "co-existency" of Soviet and Western genetics. In a short epilogue he draws attention to the philosophical consequences of his point of view, which issues in a theory of evolution by far less mechanistic than that commonly in vogue.

This little book may be warmly recommended to all geneticists who feel the need of a deeper perception of life and evolution.

Bent Harvald, Copenhagen

From the Laboratory of Human Genetics, the Psychiatric Clinic,
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RETINITIS PIGMENTOSA IN COMBINATION WITH CONGENITAL DEAFNESS AND VESTIBULOCERE-BELLAR ATAXIA; WITH PSYCHIATRIC ABNORMALITY IN SOME CASES[1]. A CLINICAL AND GENETIC STUDY[2]

By BERTIL HALLGREN

In 1951 Professor *Torsten Sjögren* interested me in making a systematic scrutiny of all the case records from the Asylum and Institute for the Blind, Lund, where a secondary disability was present. Taking this material as his starting-point, Professor *Sjögren* had himself already published some very interesting accounts of psychiatric disorders complicated with neurological and other physical disabilities, representing specific clinical and genetic entities. i.e. juvenile amaurotic idiocy (1931), congenital cataract combined with oligophrenia (1935), microphthalmos and anophthalmos with or without coincident oligophrenia (1949, in collaboration with *T. Larsson*), hereditary congenital spinocerebellar ataxia accompanied by congenital cataract and oligophrenia (1950).

Among the records I found a number of cases with retinitis pigmentosa in combination with deaf-mutism, some of which also suffered from a psychiatric disorder.

Retinitis pigmentosa can be produced by six different genes, and in all probability even more. A special gene mutation is probably responsible for the condition when it is combined with congenital deafness, and it was

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therefore of interest to make a combined clinical and genetic study of this syndrome.

Previous investigations have shown that retinitis pigmentosa and deaf-mutism are associated more often than is to be expected from their separate frequencies in the general population. As early as 1858 *v.Graefe* described their combined occurrence in three sibs. *Julia Bell* (1933) reviewing the literature reported that 10.4% out of 919 cases with retinitis pigmentosa also suffered from deaf-mutism or deafness. *Lindenov* (1945) found retinitis pigmentosa in 28 (5.8%) out of 480 cases of deaf-mutism investigated by him. 4 of these were mentally defective and all of them were reported to have "a swinging or a swaying gait". The incidence of retinitis pigmentosa in the general population is estimated to be about 0.01% (cf. *Kemp* 1951) and that of deaf-mutism about 0.05% (*Lindenov* 1945). According to *Lindenov* the incidence of retinitis pigmentosa in combination with deaf-mutism amounts to approximately 0.003%. The two symptoms when occurring together appear to be recessively inherited. It is, however, not quite clear whether they are the effect of a single gene difference or whether there is a close linkage between two different recessive genes.

Lindenov (1945) made a census investigation of deaf-mutes in 7 Danish counties. After excluding 3 cases with acquired and "unclassifiable" deaf-mutism, he found 25 individuals belonging to 10 pedigrees with coincident retinitis pigmentosa. He made a genetic analysis of this representative material using *Weinberg*'s sib method. The parental mating was unaffected × unaffected in all instances. The observed morbidity rate for retinitis pigmentosa was 27.4 ±3.4%. All but one of the affected cases were deaf-mutes too. Further, there were 3 deaf-mutes without ophthalmological symptoms. The result fits best the hypothesis of a single recessive gene with a pleiotropic manifestation. The possibility of a close linkage of two genes can not be excluded, but seems less likely.

As was mentioned above, the primary cases of the present series were derived in the first place from the Asylum and Institute for the Blind, Lund. At this institution 26 primary cases were found. It was possible to enlarge this series by studying the case records from the elementary schools and vocational training schools for deaf persons in Sweden. 37 additional cases of congenital deafness with retinitis pigmentosa have so far been found from these sources.

The field studies so far carried out by the author have disclosed a further 25 secondary cases. The whole series to date comprises 88 cases belonging to 49 families. The genealogical research, which is still incomplete, has shown that these families belong to 44 pedigrees.

Preliminary clinical analysis

Of the 88 cases on which the preliminary analysis is based (cf. Table 1), the large majority have been examined by an ophthalmologist, and of the 76 cases still living, 53 so far have been examined personally by the author. Because the investigation is still incomplete, it is not yet possible to make a detailed clinical analysis, but it may be of interest to report certain observations at this stage.

All affected individuals aged 10 years or over so far examined by the author have been found to be suffering from both retinitis pigmentosa and congenital deafness. Of the other cases, one was reported to be deaf-mute without any ophthalmological symptoms, and two to be suffering from retinitis pigmentosa without any hearing defect. Cataract was present in 11 cases and gait disturbances of a vestibulocerebellar type in all cases about whom information on this symptom was available. 26/88 (29.5%) of the affected cases against 2/146 (1.4%) of the unaffected sibs were mentally defective. Psychosis of a schizophrenia-like type was diagnosed in 6/67 (9.0%) of the affected cases and in 1/22 (5%) of the unaffected sibs who had reached the age of 20. Thus retinitis pigmentosa with deaf-mutism seems to be associated both with mental defect and with psychosis, whereas the incidence of neither of these mental abnormalities among the unaffected sibs differs appreciably from that to be expected in the general population – cf. *Larsson* and *Sjögren* (1954). The number of observations is, however, small.

Electroretinographic studies of some of the parents, in the search for heterozygous manifestations, have not yielded any positive results.[3] Audiometric examination of suspected heterozygotes is in progress in collaboration with *B. Barr*, M.D. at the Audiological Clinic, Karolinska sjukhuset.

Preliminary genetic analysis

The disorder shows a striking familial incidence. In 21 of the 49 families there is more than one affected member.

The sex ratio among the affected individuals is normal: 43 are males and 45 females.

None of the parents suffered from retinitis pigmentosa or deaf-mutism. There were two mentally defective and two psychotic parents, belonging to four families.

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[3] Performed by *Birgitta Zetterström*, M.D. of the Ophthalmological Clinic at Karolinska sjukhuset.

Table 1. Survey of the Families.

Number and Sex	P = Propositus S = Secondary Case	Year of Birth	R = Retinitis pigmentosa, D = Congenital deafness, Md = Mental deficiency, Ps = Psychosis	Case	Father	Mother	Unaffected Sibs	Md = Mental deficiency Ps = Psychosis C = Cataract
1.	2.	3.	4.	5.	6.	7.	8.	9.
1a♀	P	1919	R D	38	60	57	♀35, ♂0†, ♀33, ♂31, ♀28, ♀26, ♂24, ♂20, ♀16, ♀13	Parents related 3:
2a♂	P	1904	R D Md	53	62†	81†⎤		2a = C, ♀60 = M
2b♀	S	1887	D	7†	62†	81†⎥ ♂72, ♂59†, ♀24†, ♀60,	Parents related
2c♀	S	1889	R D Md	65†	62†	81†⎥ ♀58, ?0†, ♂0†	2:2, 2:2
2d♀	S	1892	R D Md	64	62†	81†⎦	
3a♂	P	1924	R D	33	66	59	♀34, ♂31, ♀29, ♂25, ♂22	
4a♀	P	1889	R D	35†	60†	77†⎤	
4b♂	S	1882	R D	43†	60†	77†⎥ ♀80, ♂77, ♀64†, ♂63, ♀58	
4c♀	S	1887	R D	69	60†	77†⎥	
4d♂	S	1891	R D	66	60†	77†⎦	
5a♂	P	1928	R D	29	34†	58	♀30, 27♀	Parents related 3:
6a♂	P	1915	R D Md	42	84	82†⎤	Mother = Md,
6b♀	S	1896	R D Md	61	84	82†⎬ ♂59, ♂54, ♀50, ♂47	6a = C, 6b = C,
6c♂	S	1900	R Md	57	84	82†⎦	Parents related 2:
7a♂	P	1924	R D	33	62	59	♀31, ♀27	Parents related 2:
7b♀	S	1921	R D	36	62	59		
8a♂	P	1921	R D	36	66	67	♀38, ♂30, ♀28, ♀24, ?0†	
8b♀	S	1923	D	2†	66	67		
9a♀	P	1923	R D	34	72	68	♂48, ♂8†, ♀16†, ♀1†, ♀36	
10a♂	P	1923	R D Md	33	63	55	♀31, ♀29, ♀25, ♂18, ♀13	10b = C
10b♂	P	1941	R D	16	63	55		Parents related 2:
11a♂	P	1897	R D	60	68†	72†⎰ ♀52†, ♂46†, ♀53,	
11b♂	P	1900	R D Ps	57	68†	72†⎱ ♀46, ♀26†	
12a♂	P	1877	R D Ps	57†	62†	45†	♀60†, ♂74, ♀72	
13a♀	P	1886	R D	13†	82†	68†⎱ ♂52†	
13b♀	S	1889	R D	18†	82†	68†⎰	Parents related 2:
14a♂	P	1876	R D Md	33†	79†	68†⎤	
14b♀	S	1857	R D	65†	79†	68†⎬ ♂63†, ♀79†, ♀69†	Parents related 2:
14c♀	S	1873	R?	30†	79†	68†⎦	
15a♀	P	1913	R D	44	56†	70	♀48, ♀40, ♂35	15a = C
16a♀	P	1921	R D Md	35	67	61†⎤	
16b♂	S	1918	R D	38	67	61†⎬ ♀37, ♀32	16c = C
16c♂	S	1917	R D	40	67	61†⎦	
17a♀	P	1907	R D	50	59†	74	♂44, ♀34	
18a♀	P	1910	R D Md	47	76†	56†		18a = C Parents related 2:
19a♂	P	1923	R D	34	89	79		
19b♂	S	1898	R D Md	58	89	79		
19c♂	S	1905	R D Md	51	89	79	♀57, ♀53, ♀19†, ♂44,	19b = C, 19c =
19d♂	S	1910	R D Md	46	89	79	♀42, ♂39	
19e♀	S	1920	D	37	89	79		
20a♂	P	1905	R D	52	56†	65†⎰ ♂55, ♂50, ♂47, ♀45	
20b♀	S	1925	R D	32	56†	65†⎱	
21a♀	P	1907	R D	50	74†	80	♂1†, ♂53, ♂52, ♂47,	
21b♀	P	1901	R D Ps	56	74†	80	♀0†, ♂45, ♀43, ♀39	
21c♂	S	1916	R D Ps	41	74†	80		Mother = Ps

Number and Sex	P = Propositus S = Secondary Case	Year of Birth	R = Retinitis pigmentosa, D = Congenital deafness, Md = Mental deficiency, Ps = Psychosis	Case	Father	Mother	Unaffected Sibs	Comments (Md = Mental deficiency, Ps = Psychosis, C = Cataract)
1.	2.	3.	4.	5.	6.	7.	8.	9.
2 a♀	P	1916	R D Ps	41	65†	74†	♂56, ♂3†, ♂50, ♀48	
3 a♂	P	1902	R D Ps	55	—	62†		Mother = Ps, 23a = clubfoot
4 a♀	P	1922	R D	35	60	60	♀32, ♂28	24a = C
5 a♀	P	1944	R D	13	42	33	♀8, ♀6	
6 a♀	P	1942	R D Md	15	—	49		Mother = Md
7 a♂	P	1930	R D	27	76†	50	♀31, ♂29, ♀24, ♂22	
8 a♀	P	1933	R D	24	53†	67		
8 b♀	P	1936	R D	21	53†	67		
8 c♀	S	1920	R D	37	53†	67	♂38, ♀30, ♂16†	
8 d♂	S	1924	R D	33	53†	67		
9 a♀	P	1938	R D	19	47	46		
9 b♂	P	1945	R D	12	47	46		
0 a♀	P	1937	R D Md	20	55	45		Parents related 3:3
1 a♂	P	1939	R D	18	42†	37	♂4	Parents related 3:3
1 b♀	P	1945	R D	12	42†	37		
2 a♂	P	1934	R D	23	60	45	♀22, ♀12	
3 a♂	P	1903	R D Md	54	—	72		33a = C
4 a♂	P	1942	R D Md	15	34	35		
5 a♀	P	1919	R D Md	35†	63†	60†	♀30, ♀28, ♂22 (genealogy incomplete)	♀28 = Md + Ps
5 b♀	P	1922	R D Md	35	63†	60†		
5 c♀	S	1927	R D	30	63†	60†		
5 d♂	S	1931	R D Md	26	63†	60†		
6 a♂	P	1933	R D	24	64	61	♂30	
7 a♀	P	1935	R D	22	53	45		
7 b♂	P	1941	R D	15	53	45	♂25, ♀23, ♀19, ♀17	
7 c♂	P	1943	R D	14	53	45		
7 d♂	P	1945	R D	12	53	45		
8 a♀	P	1934	R D	23	67	63	♂0†, ♀25	
9 a♀	P	1941	R D	16	40	56		
0 a♂	P	1922	R D Md	35	65	27†	♀32, ♀31, ♂1†, ♂28	
1 a♀	P	1947	R D	9	33	30	♂8, ♂5	
2 a♀	P	1923	R D Md	34	50†	61	♀37, ♀36, ♀32, ♂27,	
2 b♀	P	1936	R D Md	20	50†	61	♂0†, ♀22	Parents related 2:2
2 c♂	P	1928	R D	28	50†	61		
3 a♂	P	1926	R D Md	31	59	57	♀28	
4 a♂	P	1923	R D	34	63	58	♂30	
5 a♀	P	1947	R D	10	40	37	♀15, ♂8	
6 a♂	P	1907	R D Md	50	—	72†	(genealogy incomplete)	
6 b♂	P	1916	R D Md	41	—	72†		
7 a♀	P	1931	R D	25	52	49	♀27, ♂23, ♂21, ♂19,	Parents related 2:3
7 b♀	P	1942	R D	15	52	49	♂13, ♀10	
8 a♀	P	1937	R D	19	56	48	♂13	Parents related 2:2
9 a♂	P	1939	R D	18	51	44	♀19, ♀12, ♀9	

Table 2. Genetic Statistical Analysis with Weinberg's Propositus Method.
Parental Mating: Unaffected × Unaffected.

No of families	$\sum n_i$	47
Of which families with one child only		7
No of children	$\sum s_i$	213
No of affected children	$\sum x_i$	82
No of propositi	$\sum y_i$	59
No of sibs of propositi	$\sum y_i \ (s_i-1)$	238
No of affected sibs of propositi	$\sum y_i \ (x_i-1)$	58
Mendelian ratio	$100 \dfrac{\sum y_i \ (x_i-1)}{\sum y_i \ (s_i-1)} = P$	24.3%
Standard error	$\sqrt{\dfrac{P \ (100-P)}{\sum s_i - \sum n_i}}$	± 3.3%

The incidence of first-cousin marriages among the parents was high i.e. 20%. In a further 5 families they were more distantly related (cf. Table 1).

A preliminary genetic-statistical analysis with *Weinberg*'s propositus method (1925) has been performed on 47 families about whom adequate information is available. When all cases of retinitis pigmentosa and congenital deafness are included, the morbidity risk is found to be $24.3 \pm 3.3\%$ (cf. Table 2).

Taken together, these results plainly indicate that the disorder is due to a single recessive gene mutation which manifests itself in retinitis pigmentosa as well as in congenital deafness. There also seem to be associations between these two symptoms and mental deficiency and psychosis. A full analysis must, however, be postponed until the collection of the primary data is complete.

Calculations will later be made *inter alia* of the distribution of the affected according to position in family, the morbidity risk among the sibs in families of different sizes, mortality, mutation rate and incidence of the disorder in the general population. Furthermore, the probable heterozygous lines will be followed up.

Summary

A preliminary report is made of a clinical and genetic investigation of the rare syndrome retinitis pigmentosa, congenital deafness and spino-cerebellar ataxia, with psychiatric disorder in some cases. The series consists of 88 cases belonging to 49 families.

All affected individuals who had reached the age of 10 and had been examined by the author suffered from both retinitis pigmentosa and congenital deafness. Cataract occurred in 11 of the cases with retinitis pigmentosa. All affected individuals about whom information was available showed gait disturbances of a vestibulocerebellar type, 30% were mentally defective and 9% suffered from psychosis.

The genetic analysis plainly indicates that the disorder is due to a single recessive gene mutation which manifests itself in retinitis pigmentosa as well as in congenital deafness. There also seems to be a relationship between these two conditions and mental deficiency and psychosis.

Zusammenfassung

Die Verfasser legen eine vorläufige Mitteilung über eine klinische und genetische Erforschung des seltenen Syndromes Retinitis pigmentosa, angeborene Taubheit und spinocerebelläre Ataxie vor. Das Syndrom geht in manchen Fällen mit geistigen Störungen einher. Die Serie besteht aus 88 Fällen, die zu 49 Familien gehören.

Alle erkrankten Personen, die das Alter von 10 Jahren erreicht hatten und die der Verfasser untersuchen konnte, litten an Retinitis pigmentosa und angeborener Taubheit. Eine Katarakt fand sich bei 11 der Retinitis pigmentosa-Fälle. Alle erkrankten Personen, von denen Information vorhanden war, zeigten Gangstörungen vom vestibulocerebellaren Typ, 30% waren geistig zurückgeblieben und 9% hatten eine Psychose.

Die genetische Analyse zeigt klar, daß die Krankheit durch ein einziges rezessives Gen hervorgerufen wird, das sich in der Retinitis pigmentosa wie in der angeborenen Taubheit manifestiert. Außerdem scheint eine Beziehung zwischen diesen beiden Symptomen, geistigem Defekt und Psychose zu bestehen.

Résumé

Rapport préliminaire concernant les examens cliniques et génétiques d'un syndrome rare: rétinite pigmentaire, surdité congénitale et ataxie spino-cérébellaire, associée à des troubles psychiatriques dans quelques cas.

Le matériel se compose de 88 cas appartenant à 49 familles. Tous les individus d'au moins 10 ans et examinés par l'auteur ont présenté une rétinite pigmentaire avec surdité congénitale. Une cataracte a été observée dans 11 cas atteints de rétinite pigmentaire. Sur le total des individus dont on a pu obtenir des informations, tous présentaient des troubles de la démarche, 30% des troubles mentaux et 9% une psychose. L'analyse génétique parle nettement en faveur de l'idée qu'il s'agit d'une mutation récessive simple et que ce gène est responsable aussi bien pour la rétinite pigmentaire que pour la surdité. Il semble y avoir une relation directe entre ces 2 affections, le retard mental est la psychose.

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PERNICIOUS ANEMIA IN MONOVULAR TWINS

By JENS CHR. ARBO

with a note on zygosity

by JAN MOHR

Introduction

For more than 60 years the tendency of pernicious anemia (p.a.) to familial occurrence has been conspicuous. This tendency is now firmly established by numerous case reports and by several recent investigations.[1,2,3] However, while there seems to be general agreement that the disease is familial, the reported incidence among relatives varies very considerably.

The most important recent study in this field seems to be that of *Mosbech* (1953)[2], who made a thorough investigation of the relatives of 234 patients having a definitely established diagnosis of p.a. Among approximately 3000 relatives the disease occurred about 20 times as frequently as in a normal series. An analysis of the distribution of p.a. among the relatives proved compatible with irregular recessive inheritance, although irregular dominance could not be ruled out. A slight preponderance of females was found. *Mosbech* presumed the disease to develop as a result of the joint action of endogenous and exogenous factors, and the inherited defect to be localized in the gastric mucosa. A simple mode of inheritance seemed unlikely.

Pernicious anemia in monozygotic twins

Studies of monovular twins may help our understanding of the genetics of p.a. by giving information on the frequency of manifestation of the relevant genotype and the possibilities of modification of the manner of

manifestation by environmental factors. The absence of knowledge on the mode of selection of the twin material, however, often detracts from the value of such studies.

Because of the relatively rare occurrence of the disease and its late manifestation, the number of monozygotic twins developing p.a. is, however, too small to give more than a limited knowledge.

For an account of earlier reports on p.a. in monovular twins, the reader is referred to *Mosbech* (1953)[2], who found 8 adequately substantiated cases in the literature. The disease occurred concordantly in 6 of them. Among the 8 pairs, 5 were female and 3 male. The age at onset of p.a. varied from 36 to 85 years. In 2 cases the disease developed simultaneously in both twins, while in the other 4 there was a difference in age at onset varying from 1 to 9 years.

The present author has not been able to find further reports on p.a. in monovular twins in the available literature.

In the following an additional concordant case, encountered by chance in a hospital department, will be presented.

<div style="text-align:center">The present case</div>

Family

The *mother* of the twins had always been in good health and died of old age. The twins were her only children. Nothing is known about her family.

The *father* died of an unknown abdominal disease when the twins were 4 years of age. He had formerly enjoyed good health and belonged to a healthy family, in which there had been frequent occurrence of twins in earlier generations. His father had two twin sisters.

There had been no known cases of blood diseases or hereditary diseases in the family.

The patients

The twins, *O.S.* and *J.R.*, both female, were born 2. 12. 1876 in *Meldal, Norway*. The twins always showed a striking resemblance; as small children they were "as like as two peas". When first seen by the author, the twins were 77 years old but still looked very much alike, *J.R.* having slightly coarser features than her sister. (See photographs, Fig. 1, 2 and 3.) Both had the same stocky, "pyknic" habit and the same (ample) degree and distribution of adipositas. *Stature and weight: (O.S.)* 156 cm., 75.8 kg.; *(J.R.)* 154 cm., 75 kg. They both had straight, dark brown *hair* of identical colour. The *eye colour* showed the same brown shade and their *iris patterns* were very similar. It was interesting to note that both twins had developed the same degree of *Dupuytren's contracture* bilaterally. Even the patterns of the superficial veins on their forearms and legs were almost identical.

<div style="text-align:center">History</div>

Case 1. O.S. J.n. 144/56.

The patient was a farmer's widow and had given birth to 6 children. As a child she had diphteria and in her youth pleurisy. During the last 10 years preceding her first admission to hospital, she had suffered from periodic attacks of colicky pain in the upper,

Fig. 1

O.S.   J.R.

The twins, aged 14

Fig. 2

Fig. 3

O.S.   J.R.

The twins, aged 79

right quadrant of abdomen, supposed to be due to gall-stones. For many years she had been chronically obstipated and had shown intermittent symptoms of cystitis.

In the *autumn of 1953* (aged 76) she consulted her physician, complaining of fatigability, weakness and anorexia. Hemoglobine level was 75%. After iron medication, the hemoglobine level in March 1954 was 90%, decreasing to 70% during May 1954, accompanied by

Table I

Case 1. O. S.

Clinical and relevant laboratory data

	1st stay in O. Hosp. May 1954	2nd stay in O. Hosp. March-April 1955		3rd stay in O. Hosp. (Medical department) January-March 1956		
		Before treatment	After treatment*	On admission	After withdrawal of treatment (2 months)	After renewed treatment*
Pallor	·|····|·|·|	Moderate	·|····|·|	·|··|··|···	··|····|·	·|··|··|·
Weakness		Moderate				
Palpitations		Moderate				
Dyspnoea		Slight				
Tongue	Slightly red.	Unchanged	Unchanged	Unchanged		Unchanged
CNS	Atrophy of papillas Loss of Achilles tendon refl. bilat.	Unchanged	Unchanged	Right: (+)? Left: ++		
Hemoglobine	73%	65%	73% (within 8 days)	105%	88%	100%
RBC	3.44 mill.	2.93 mill.		4.17 mill.	3.82 mill.	
Colour Index	1.06	1.11		1.26	1.15	
Reticulocytes			4% (5th day) 5% (7th day)			2.3%
WBC	3300	2100		4900	4600	
Blood film	Preponderance of lymphocytes	Aniso-, macro-, poikilocytosis. Leucopenia. Relat. lymphocytosis. Polymorphs with hypersegm. nuclei. 8				
Icterus Index						
Sternal bone-marrow		Some typical megaloblasts. Moderate depression of leucopoiesis with giant forms of stab cells and immature forms.				
Ewald's test	Congo ÷ Acidity 0/5.					Achlorhydria
Histamine test						
X-ray						
Stomach-Duodenum	Negative	Negative		Negative		
Urinalysis	Negative	Negative		Negative		
Stool	Negative					

Table II

Case 2. J. R.

Clinical and relevant laboratory data

	2nd stay in O. Hosp. February-March 1954		On admission	3rd stay in O. Hosp. (Medical department) February-March 1956	
	Before treatment	After treatment*		After withdrawal of treatment (2 months)	After renewed treatment*
Pallor	Pronounced				
Weakness	Pronounced				
Palpitations	Marked				
Dyspnoea	Moderate				
Tongue	Slightly smooth along the edges.	Unchanged	Unchanged		Unchanged
CNS	No signs of CNS changes				
Hemoglobine	43%	Unchanged 75% (with-in 20 days)	Unchanged 98%	88%	Unchanged 100%
RBC	1.64 mill.		4.45 mill.	3.95 mill.	
Colour Index	1.31		1.10	1.11	
Reticulocytes		4.4% (5th day)			
WBC			3900	4300	
Blood film	Pronounced aniso-, macro-, poikilocytosis. Diff. count normal			Preponderance of lymphocytes (51%). Slight aniso-, macrocytosis, polychromatophilia. Some hypersegm. of polymorphs.	
Sternal bone-marrow				Loose structure of nucleated red cells. A few characteristic megaloblasts. Some giant band forms, hypersegm. polymorphs and marked increase in number of lymphocytes and retic. cells.	
Ewald's test Histamine test	Congo ÷ Acidity 0/4		Achlorhydria		
X-ray Stomach-Duodenum-Thorax	Negative				
Urinalysis	Bacteri-, pyuria.	Negative	Negative		
Stool	Negative		Negative		Negative

* I.m. injections of liver extract (Pernami "NYCO") 5.5 ml. twice weekly.

progressive fatigability, weakness, loss of appetite and symptoms of cystitis. There was no ataxy, acroparesthesia or subjective tongue-manifestations.

For further clinical and relevant laboratory data from 3 subsequent periods in Orkdal Hospital, the reader is referred to *Table I.*

Case 2. *J.R. J.n. 142/56*

The patient was a farmer's wife and had given birth to 3 children, – one abortion. Her husband and 2 daughters were healthy. 1 boy died a few weeks old.

At 24 years of age she had a pulmonary infection with fever of a few weeks duration. (Probably tuberculous infection, - cp. twin sister's pleurisy.) After that time she enjoyed good health, apart from a tendency to chronic obstipation for many years.

December 1946 the patient noticed a lump in the left breast, and had her first stay in Orkdal Hospital, February – March 1947.

There was a palpable tumour in the left breast above the nipple. The hemoglobine level was normal. The tumour was locally excised, but as the cytological diagnosis proved to be *duct carcinoma*, radical operation was performed. During operation two hard axillary lymph nodes were encountered, supposed to be metastases. The cytological diagnosis, however, was *tuberculous lymphadenitis.* She was given postoperative X-ray irradiation and later controls showed no signs of recurrence.

During the years *1952–53* she complained of fatigability, weakness, slight giddiness and dyspnoe, with mild attacks of anginoid pain. Her physician found a hemoglobine level about 90%.

January 1954 (aged 77) she was confined to bed with weakness, pallor, loss of appetite, slight fever, obstipation and a bad physical condition. For further clinical and relevant laboratory data from 2 subsequent periods in Orkdal Hospital, the reader is referred to *Table II.*

During their last stay in hospital photographs were taken of the twins, and samples of blood, sputum and skin imprints were obtained, in order to establish the probability of monovularity. *J. Mohr*, at the University Laboratory of Human Genetics, Oslo, Norway, kindly analysed the material and completes this paper with a note on zygosity, concluding that the case for monovularity appears good.

Discussion

In this case of probably monovular twins, both members – at about the same age (77) – insidiously develop the clinical picture of moderate anemia. During subsequent periods in Orkdal Hospital several characteristic common features are found:

1. Slight or more pronounced, atrophy of the tongue papillas.

2. Moderate or more pronounced, hyperchromic anemia.

3. Blood film: Macrocytosis, anisocytosis, poikilocytosis and chromatophilia. Leucopenia, with a relative lymphocytosis.

4. Sternal bone-marrow smear: Few, but characteristic, megaloblasts.

5. Histamine fast achlorhydria.

6. Reticulocyte response and normalization of hemoglobine level following the administration of potent liver extract, with corresponding complete relief of all general symptoms. (No iron therapy given.)

7. Decrease of hemoglobine level following temporary withdrawal of liver extract and again favourable response following recommencement of liver extract therapy.

8. Stool normal and benzidine negative. X-ray examination of stomach and duodenum negative.

These findings seem to justify a diagnosis of p.a. in both cases. Only one of the twins showed slight signs of C.N.S.-affection (loss of Achilles tendon reflexes).

Nearly two years have now passed since their last stay in hospital and their physician reports that the twins are receiving regular liver extract preparations. Hemoglobine level and blood picture is normal in both cases.

It is interesting to note that the twins also demonstrate concordant occurrence of Dupuytren's contraction bilaterally and discordant occurrence of duct carcinoma of the breast.

Note on zygosity

The results of the examination of blood samples, the prints of the skin patterns, and the hair samples, were as follows:

Blood

Both twins A_1 MS R_2r Le (a+) Lu (a—) p Fy (a+) k Jk (a+).

Fingerprints

O.S.					J.R.				
1.	2.	3.	4.	5. finger	1.	2.	3.	4.	5. finger
R. $L_u 8$	$L_u 6$	$L_u 7$	–	$L_u 3$	R. $L_u 11$	$L_u 10$	$L_u 9$	$L_u 5$	$L_u 9$
L. $L_u 5$	$L_u 4$	$L_u 4$	$L_u 5$	$L_u 9$	L. $L_u 6$	$L_u 4$	$L_u 4$	$L_u 14$	$L_u 10$

The L_u's in these formulae for the fingerprints denote ulnar loops, the adjoined numbers the ridge counts for the respective fingers. The sum of these counts, the total ridge count, is 51 for O.S., 77 for J.R. The right fourth finger was left out in this count for both twins, since print of this finger was lacking in the case of O.S.

Palm prints, main lines

O.S. The A-line on both sides ends within the distal third of the ulnar margin of the palm. The right B-line ends in field 8 (i.e. at the root of the fourth finger), the left in field 7

(between fourth and fifth finger). The right C-line ends in field 10 (root of third finger), the left in field 9 (between third and fourth finger). The right D-line ends in field 11 (between second and third finger), as does the left D-line.

J. R. The A-line on both sides ends within the distal third of the ulnar margin of the palm. The right B-line ends in field 8, the left in the distal third of the ulnar margin of the palm. The right C-line ends in field 10; the left is difficult to trace but may end in field 9. The right D-line seems to end in field 11, the left in field 9.

Palm prints, ridge patterns

O. S. The thenar fields show no patterns, the hypothenar fields a radial loop on the right side, an uncomplicated pattern on the left. Field 7 no pattern on the right hand, a rudimental pattern on the left. Field 9 a rudimental radial loop on both sides.

J. R. Left thenar field no pattern, right undiscernable. Hypothenar field radial loop on the right hand, no pattern on the left. Field 7 rudimental loop on left side, indiscernible on right. Field 9 rudimental loop on the right hand, indiscernible on left.

Toe prints

O. S. Big toe ulnar loop on both sides, the prints of the other toes not classifiable with certainty, although parts of the patterns appear clearly on all toes.

J. R. Big toes ulnar loop on both sides, very similarly shaped to those of O. S. Patterns of the other toes not classifiable with certainty. The part of the patterns that appears clearly, shows some points of more conspicuous similarity than ordinarily found between sibs.

Sole prints

O. S. S-fields (proximal to the big toe) ulnar loop on right, radial loop on left. The other fields of the sole not classifiable with certainty.

J. R. S-fields whirl on right foot, distal loop on left. The rest of the fields not classifiable with certainty.

Hair samples

Both twins had dark brown hair (T on the Fischer-Saller scale). The samples were so similar in colour that they might have been taken from the same head.

Other traits

A number of additional observations relevant to the diagnosis of zygosity, such as similarity in stature and weight, eye colour, iris pattern, pattern of superficial veins, as well as concordance of a pathological condition, namely Dupuytren's contracture, have been made by Arbo (see page 106 and fig. 1, 2, 3).

Probability of monovularity

From the identity of the blood groups in all the nine systems that were

examined, it may be calculated (*Smith* and *Penrose*, 1955) that the relative chance of dizygosity in the present case is 0.0315.

The fingerprints of the two twins show striking resemblance as do the palm prints. The hair samples are of identical colour. The photographs show a higher degree of similarity than ordinarily found in binovular twins or usual sibs, which also applies to the observations on stature and weight.

The concordance, also as regards degree of development, of Dupuytren's contracture, suggests a closer genetic similarity than between binovular twins.

Conclusion

It appears almost certain that the twins are monovular.

Summary

A case of pernicious anemia in both members of monovular, female twins is described.

Zusammenfassung

Mitteilung eines Falles von perniciöser Anämie bei eineiigen weiblichen Zwillingen.

Résumé

Une anémie pernicieuse a été constatée chez deux jumelles univitellines.

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TASTE SENSITIVITY TO PTC IN 60 NORWEGIAN FAMILIES WITH 176 CHILDREN. CONFIRMATION OF THE HYPOTHESIS OF SINGLE GENE INHERITANCE

By BRITA BRANDTZÆG MERTON

Introduction

Since the detection of the variability of human individuals in taste sensitivity to phenylthiocarbamide (*Fox.* 1931), extensive studies have been carried out with regard to the influence of heredity on this character. The theory first put forward (*Snyder.* 1931; 1932; and *Blakeslee* and *Salmon*, 1931), implies recessive inheritance of the non-taster trait. However, some doubt was raised about this theory in the recent works of *Harris* and *Kalmus* (1951) and to some extent by *Das* (1956). They studied the distribution of PTC taste-thresholds of sib-pairs, applying the sorting technique of *Harris* and *Kalmus* (1949). Besides testing the hypothesis of simple, recessive inheritance, they tested the hypothesis that the variation is the result of just a chance combination without any influence of heredity. The investigation of *Harris* and *Kalmus* failed to confirm either the genetical hypothesis or the chance combination theory. The analysis undertaken by *Das* indicates that neither hypothesis is in confirmity with the observed frequencies, but in respect of the extreme tasters and non-tasters he obtained a satisfactory agreement with the theory of recessive inheritance.

No other hypothesis has been put forward to explain the observed variation in taste ability, and the doubt whether the existing theory is entirely adequate has suggested the desirability of further research.

The purpose of the present paper is to contribute to the knowledge of the heredity of the PTC taste character by testing the hypothesis of simple,

recessive inheritance on a family material, comprising parents and children. It became then necessary also to estimate the frequency of nontasters in Norway. All the data have been obtained by applying the sorting technique developed by *Harris* and *Kalmus* (1949)

The present paper also includes data on linkage relations between the PTC taste character and the blood groups ABO, MN, Rh, Le, Lu, P, Fy, K and Jk, analysed by the method introduced by *Finney* (1940).

The frequency of non-tasters in Norway

Technique

The technique of *Harris* and *Kalmus* was used with a slight modification. As stock solution was used No. 3 of *Harris* and *Kalmus*, containing 0.325 gr l. Distilled water was used both in the tests and for the preparation of the solutions.

Table I. Taste thresholds for PTC of 181 males classified by age

Age in years	Solution No.															Total
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
16–17	–	2	–	–	–	–	–	–	–	–	1	1	–	–	1	5
18–19	2	–	1	2	3	–	–	2	3	7	11	–	–	1	–	32
20–21	4	–	4	4	4	–	3	1	8	11	12	2	–	2	–	55
22–23	2	2	–	1	5	–	1	2	2	6	1	1	–	–	–	23
24–25	–	2	1	1	1	–	2	–	2	2	–	–	–	–	–	11
26–27	1	–	–	1	2	–	–	–	2	–	1	–	–	–	–	7
28–29	–	–	–	1	1	–	–	–	1	2	1	–	–	–	–	6
30–31	–	–	2	–	–	–	2	–	1	–	1	–	–	–	–	6
32–33	–	1	–	–	–	–	1	1	–	–	1	–	–	–	–	4
34–35	–	–	–	–	–	–	–	1	–	–	2	1	–	–	–	4
36–37	–	1	–	–	1	–	1	–	1	1	–	1	–	–	–	6
38–39	–	–	–	–	–	–	–	1	1	2	1	–	–	–	–	5
40–41	–	–	–	–	–	–	–	1	2	1	–	–	–	–	–	4
42–43	–	–	–	1	–	–	–	2	–	–	–	–	–	–	–	3
44–45	–	–	1	–	–	–	1	–	2	–	–	1	–	–	–	5
46–47	–	1	–	–	–	–	–	–	–	1	–	–	–	–	–	2
48–49	–	1	–	–	–	–	–	–	–	–	–	–	–	–	–	1
50–51	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
52–53	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
54–55	–	–	1	–	–	–	–	1	–	–	–	–	–	–	–	2
Total	9	10	10	11	17	–	11	12	25	33	32	7	–	3	1	181

Table II. Taste thresholds for PTC of 85 females classified by age.

Age in years	Solution No.															Total
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
16–17	–	–	–	–	–	–	–	–	1	–	1	–	–	1	2	5
18–19	1	1	1	–	1	–	2	–	–	2	3	–	–	–	–	11
20–21	–	–	2	–	2	–	–	–	–	2	3	1	–	–	–	10
22–23	–	1	–	1	–	–	–	–	–	3	1	1	–	–	–	7
24–25	–	–	·	–	–	–	–	–	–	1	1	3	1	–	–	6
26–27	–	–	–	1	–	–	–	1	1	–	1	–	–	–	–	4
28–29	–	–	–	–	–	–	–	–	–	1	–	–	–	–	–	1
30–31	–	–	–	–	–	–	–	–	1	–	–	–	–	–	–	1
32–33	1	–	1	–	–	–	–	–	–	–	2	2	–	1	–	7
34–35	–	–	–	–	–	–	–	–	–	2	1	–	–	–	–	3
36–37	–	1	–	–	–	–	–	1	2	–	–	–	1	–	–	5
38–39	–	1	1	1	–	–	–	1	1	1	–	1	–	1	1	9
40–41	2	–	··	1	–	–	1	–	–	1	–	–	–	–	–	5
42–43	1	–	1	–	–	–	–	–	1	–	2	–	1	–	–	6
44–45	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
46–47	–	–	–	1	–	1	–	–	–	1	–	–	–	–	–	3
48–49	–	–	–	1	–	–	–	–	–	–	–	–	–	–	1	2
50–51	–	–	–	–	··	–	–	–	–	–	–	–	–	–	–	–
52–53	··	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
54–55	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Total	5	4	6	6	3	1	3	3	7	14	15	8	3	3	4	85

Material

The total number of tested, unrelated individuals were 266. The majority were students from the University of Oslo. In addition, examination was made of a group of persons between 30 and 55 years of age. Tables I and II give the distribution of taste-thresholds and the ages for all males and females tested.

Frequency of non-tasters

Earlier investigations show that there are significant differences between the average thresholds for males and females, but no sex differences are found in the frequencies of non-tasters (*Hartmann*, 1939; *Falconer*, 1946; *Harris* and *Kalmus*, 1949; *Mohr*, 1951, a). As the minimum classes for males and females coincide, in the following discussion the two sexes are put together. Figure 1 shows the distribution of the taste-thresholds for males and females.
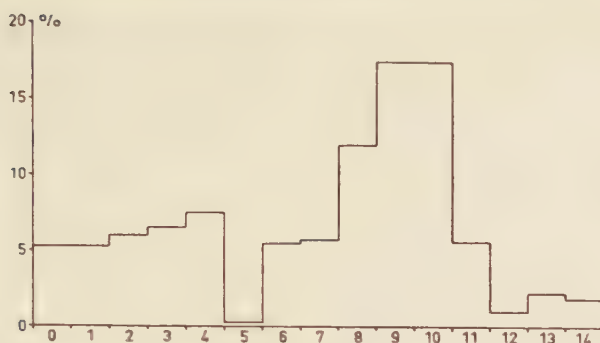
Fig. 1. Distribution of P.T.C. taste tresholds for 181 males and 85 females between the ages of 16 and 55.

The material falls into two definite parts, and the antimode of the threshold distribution is found to be at solution No. 5. Accordingly, this solution will be used to separate tasters and non-tasters. All subjects who can taste solution No. 5 or weaker, will be classified as tasters; subjects who can only taste solutions stronger than No. 5 as non-tasters.

Assuming that the borderline between the two groups lies at solution No. 5, the number of non-tasters is 81, and of tasters 181. Consequently the frequency of non-tasters in the Norwegian population will be 30.45%.

Discussion

Studies of *Harris* and *Kalmus* (1949), *Mohr* (1951, a) and others, indicate that the taste sensitivity to PTC decreases with age. Since the material used for the present study only includes individuals below 55 years of age, it was not found necessary to make any adjustments for this factor. Neither is any account taken of the possible influence of smoking. The stability of the solutions over some months was checked by repeated testing of some of the individuals. The retests yielded identical threshold-values. This seems to agree with the experience of *Blakeslee* (1932) and others.

The frequency of non-tasters has been compared with the frequencies obtained by other investigators who used the same technique. Only individuals of the same age group as in the present investigation have been taken into account. Table III gives a comparison between the frequencies of non-tasters found in England (*Harris* and *Kalmus*, 1949), Denmark (*Mohr*, 1951, a), West-Bengal (*Das*, 1956) and in the present inquiry. The borderline between tasters and non-tasters is put at the minimum class

Table III. Comparison of frequencies obtained by different investigators
with the same technique

	Nontasters	Tasters	Total	%Nontasters
Harris and Kalmus (1949)	60	127	187	32.02
Mohr (1951, a)	86	184	270	31.85
Das (1956)	154	335	489	31.49
The present paper	81	185	266	30.45
Total	381	831	1212	

$\chi^2 = 0.18$ for 3 D.F., P = 0.98

in each set of data. The data includes individuals of both sexes, except as regards the English, which consists only of males.

A χ^2-test showed no significant heterogeneity between the results of the four studies.

A similar comparison of data obtained by various techniques (Mohr, 1951, a) did not show such a close correspondence as the one found here. This is ascribed to technical rather than to biological differences, which conclusion seems confirmed by the above results. The close correspondence shown in Table III indicates the high degree of consistency and accuracy achieved by using the technique of Harris and Kalmus.

The threshold distributions, however, do not seem to correspond in the same degree. Even between distributions with the antimode at the same solution number, those found by Mohr and by the present author, a significant difference appears ($\chi^2 = 36.4$ for 9 D.F.). This deviation may be due to differences in the experimental conditions during the tests. Psychological factors, such as the subject's intelligence and attention during the test, have also been mentioned earlier as relevant for obtaining consistent results (Hartmann, 1939).

Analysis of family data

The hypothesis of simple, autosomal, recessive inheritance of the nontaster trait has been tested on a material of 60 families with 176 children. In all, 107 families were visited. Of these, 51 were selected at random, while the rest were selected by first testing the parents. Among these, only families with non-taster parents, 9 in all, were completely tested and included in the material. Children below 6 years of age were not included. Table IV gives the data, classified according to mating type and distribution of children. Phenotypic tasters are marked T+ and non tasters T—.

Table IV. Taste sensitivity to PTC in 60 Norwegian families with 176 children

Group No.	Father	Mother	No. of families	Children T+	Children T—
I	T+	T+	8	2	0
			7	3	0
			2	4	0
			1	5	0
II	T+	T+	4	1	1
			1	1	2
			4	2	1
			2	2	2
			2	3	1
III	T—	T–	1	2	0
			1	4	0
	T–	T+	1	2	0
			4	3	0
IV	T+	T–	4	2	1
			1	3	1
	T–	T+	2	1	1
			2	2	1
			1	1	2
			1	0	3
V	T–	T–	4	0	2
			2	0	3
			1	0	4
			1	1	1
			1	2	0
			1	1	5
			1	1	6

Analysis of the results

A method proposed by *R.A.Fisher* (see *Race* and *Sanger*, 1952) has been used for the analysis. Assuming that the phenotype T— represents the genotype tt, the gene frequencies may be derived as follows:

$$t = \sqrt{0.3045} = 0.5519$$

$$T = 1 - \sqrt{0.3045} = 0.4481$$

A. *Comparison of the observed and expected number of families with and without recessive children*

Mating $T+ \times T+$

The observed and expected number of families in which *all the children* are T+ is shown in Table V.

Families with some children T—: The expected number of families with T—-children is $18 \div 7.0648 = 10.9352$, while 11 were observed.

Table V. Families of the mating type $T+ \times T-$ having only $T+$-children

Size of family	No. of families	No. of families having only T+-children	
		Expected	Observed
2	4	1.8660	2
3	12	4.5324	4
4	2	0.6664	1
Total	18	7.0648	7

Mating $T+ \times T—$

The observed and expected number of families in which *all the children* are T+ is shown in Table VI.

Families with some children T—: The expected number of families with T—-children is $31 \div 22.3756 = 8.6244$, while 13 were observed.

Table VII gives a comparison of the expected and obtained values for all families with one or both parents T+.

Table VI. Families of the mating type $T+ \times T+$ having only $T+$-children

Size of family	No. of families	No. of families having only T+-children	
		Expected	Observed
2	12	9.3444	8
3	12	8.4912	7
4	6	3.9258	2
5	1	0.6142	1
Total	31	22.3756	18

Table VII. Analysis of families with one or both parents T+

Mating	Family	Expected No. of families	Observed No. of families	χ^2	D.F.
T+ × T+	All children T+	22.3756	18	3.075	1
	Some children T –	8.6244	13		
T+ × T –	All children T+	7.0648	7	0.001	1
	Some children T –	10.9352	11		

$\chi^2 = 3.076$ for 2 D.F., $0.3 > P > 0.2$

Mating T— × T—

Assuming that the hypothesis of recessive inheritance is correct, we should expect to find only non-taster children in this group. But, as shown in Table IV, four of the families have children, five children in all, of the phenotype T+. Retesting of the families yielded the same results. Their taste sensitivity was not influenced by illness or any other known factor.

Owing to the continuity of the frequency distribution of taste-thresholds, it is difficult to fix accurately the boderline between tasters and non-tasters. The genotypes do not result in two sharply separated phenotypes, and the two threshold groups overlap (*Hartmann*, 1939; *Harris* and *Kalmus*, 1951). This may cause some inaccuracy in the diagnosis of the borderline tasters and non-tasters, and might possibly be responsible for the observed difference in the present case. In all the four families concerned, one of the parents had the threshold No. 3, and perhaps some of these are genotypically tasters. Among the children one had the threshold No. 6, three had threshold No. 7 and the last one threshold No. 8. Here the opposite case is possible; some of the children may be genotypically non-tasters.

Possible influence of psychological factors will manifest itself chiefly in the testing of borderline cases. Particularly if the material is heterogenous in respect of intelligence, as in the present case.

Owing to the fact that all the subjects who do not coincide with the hypothesis have intermediate thresholds, it is reasonable to explain these as cases of misclassification of genotypes.

B. *Comparison of the observed and expected number of children in families with at least one T—-child*

The proband method of *R. A. Fisher* (1934) has been used for the calculations.

The analysis of the data is presented in Table VIII.

Table VIII. Observed and expected number of children from families containing
at least one T—-child

Mating		Children		χ^2	D.F.
		T+	T—		
T+ × T+	Expected	22.1	16.9	0.084	1
(13 families)	Observed	23	16		
T+ × T−	Expected	13.5	18.5	2.306	1
(11 families)	Observed	18	14		

$\chi^2 = 2.39$ for 2 D.F., P = 0.30

Analysis of sib-pairs

As mentioned earlier, some investigators have maintained that the
widely accepted genetic hypothesis concerning the inheritance of taste
sensitivity to PTC is open to doubt, or at least deserving of scepticism
(*Harris* and *Kalmus*, 1951; *Das*, 1956). The conclusions of these authors
are based on studies of sibpairs, tested with the technique of *Harris* and
Kalmus, and are apparently discordant with the results obtained in the
present inquiry. To ascertain whether this is due to their particular method
of analysis, the same sibpairmethod has been applied to the present data,
and the results compared with those obtained by the family method.

The material consists of 200 sibpairs, derived from:

No. of members in each sibship	2	3	4	5	6	7
No. of sibships	22	26	9	1	1	1

The whole material is presented in Table IX.

The expected number of tasters and non-tasters among the sib-pairs is found by
calculating the probabilities for the respective combinations of mating-type and children:
   1. The probability of both sibs tasters:
   The probability of a particular mating type is multiplied by the square of the probability
of a taster sib corresponding to the same mating type. Adding up these products for all six
mating types, the probability is given by

$$\frac{1}{4} (1 - q) (4 + 4q - 3q^2 - q^3)$$

where q^2 is the frequency of non-tasters.

   The expected number is found by multiplying the probability of a particular type of
sib-pair by 200.

Table IX. PTC taste thresholds for 200 sib pairs

		Elder sib: PTC solution number														
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
0	1	3	2	–	–	–	–	2	1	1	1	–	–	–	–	11
1	5	10	3	7	2	–	–	4	1	3	4	1	–	–	1	41
2	–	1	–	2	1	–	1	1	–	–	1	–	–	–	–	7
3	–	2	1	3	2	–	–	1	–	1	3	–	–	–	–	13
4	1	1	–	1	–	–	–	–	1	1	1	–	–	–	–	6
5	–	–	–	–	–	–	–	–	1	–	–	–	–	–	–	1
6	–	–	–	–	–	–	1	–	–	–	1	–	–	–	–	2
7	–	4	1	2	1	–	–	1	3	4	2	2	–	–	1	21
8	1	1	–	3	1	–	–	1	–	4	5	2	–	–	–	18
9	1	1	–	2	2	1	–	–	3	5	5	3	4	1	–	28
10	1	1	–	3	2	–	1	–	1	3	7	3	3	1	2	28
11	–	1	–	–	–	–	–	–	1	3	5	2	4	–	2	18
12	–	–	–	–	1	–	–	–	–	–	1	1	–	–	–	3
13	–	–	–	–	–	–	–	–	1	–	–	–	–	–	–	1
14	–	–	–	–	–	–	–	–	1	–	–	1	–	–	–	2
Total	10	25	7	23	12	1	3	10	14	25	36	15	11	2	6	200

(Left axis label: Younger sib: PTC solution number)

2. The probability of a taster – non-taster sibpair:
$$\tfrac{1}{4}q^2 (1-q)(3-q)$$

3. The probability of both sibs non-tasters:
$$\tfrac{1}{4}q^2 (1+q)^2$$

The expected and observed values are given in Table X.

Table X. Observed and expected frequencies of the possible four types of sib-pairs

Types of pair	Expected	Observed	χ^2	D.F.
Both sibs tasters	114.6	93		
Elder sib taster, younger sib non-taster	24.4	30	9.705	2
Elder sib non-taster, younger sib taster	24.4	29		
Both sibs non-tasters	36.6	48		

$$\chi^2 = 9.705 \text{ for } 2 \text{ D.F., } P < 0.01$$

When analysed according to this method, the hypothesis is not con-
firmed. Assuming, however, that the theory is correct, we should expect a

better agreement when regard is paid to the extreme tasters and non-tasters alone, and not to the intermediate phenotypes. *Harris* and *Kalmus* and *Das* analysed their data in this way, classifying subjects with thresholds below 5 as extreme non-tasters, and with threshold above 8 as extreme tasters. In the present case all sib-pairs, where one or both sibs have the thresholds 4, 5 or 6, are excluded. The frequencies of the possible combinations of sibpairs, consisting of extreme tasters and non-tasters, are shown in Table XI.

Also for the complete family data, a corresponding analysis of extreme phenotypes has been made, excluding families where parents or children have the thresholds 4, 5 or 6. There are 16 families of this type. The analysis of the extreme families are presented in Table XII. In the case of families of the mating type T— × T—, three families are excluded for the same reason, two of them with T+-children.

Table XI. Observed and expected frequencies of extreme tasters
and non-tasters among 176 sib-pairs.

Types of pair	Expected	Observed	χ^2	D.F.
Both sibs tasters	100.25	88		
Elder sib taster, younger sib non-taster	21.5	26		
Elder sib non-taster, younger sib taster	21.5	22	4.139	2
Both sibs non-tasters	32.75	40		

$\chi^2 = 4.139$ for 2 D.F., $0.2 > P > 0.1$

Table XII. Analysis of families consisting of extreme tasters and non-tasters,
with one or both parents T+

Mating	Family	Expected No. of families	Observed No. of families	χ^2	D.F.
T+ × T+	All children T+	17.529	15	1.35	1
	Some children T—	6.471	9		
T+ × T—	All children T+	4.621	5	0.05	1
	Some children T—	7.379	7		

$\chi^2 = 1.40$ for 2 D.F., $P = 0.50$

Discussion

The result of the analysis of families in sections A and B, with a $\chi^2 \simeq$ 3.00, P = 20–30%, show beyond doubt a satisfactory agreement with the genetic hypothesis tested. And, as expected, the analysis of the extreme families shows an even better agreement with the theory.

Analysed according to the sibpair method, the same data do not show this agreement (P < 0.01). The discrepancies obtained by *Harris* and *Kalmus* and by *Das* were even greater. By separating extreme tasters and non-tasters, *Harris* and *Kalmus* still found a significant difference, while *Das* obtained a satisfactory agreement (P $\simeq$ 0.2).

Thus, comparing the results obtained by the sibpair method and by analysing complete family data, we tend to arrive at quite discordant conclusions. The reason is probably of statistical rather than biological nature, the sibpair method being not strictly correct, except for sibpairs of only two sibs.

The present study of 60 complete families has shown satisfactory agreement with the genetic hypothesis, assuming that the major part of the variability in taste sensitivity to PTC is due to a simple, autosomal, Mendelian gene pair.

Study of linkage between PTC and the blood groups

In the present paper linkage relations between PTC and the blood groups AB0, MN, Rh, Le, Lu, P, Fy, K and Jk respectively, are studied. In accordance with the previous conclusion a simple recessive mode of inheritance was assumed for the non-taster trait. The method developed by *Finney* (1940) was applied. Earlier studies of linkage between the factors concerned have not led to any positive indication of linkage (*Boyd* and *Boyd*, 1941; *Finney*, 1941; *Snyder, Baxter* and *Knisely*, 1941; *Kloepfer*, 1946; *Race, Holt, Thompson* and *Sanger*, 1952; *Mohr*, 1954; and others). On the other hand, the published data are not sufficient to exclude even rather close linkages with certainty. Additional material is therefore needed.

The blood group data had been collected earlier by others, at the Human Genetics Laboratory, University of Oslo.

The material analysed for linkage consists of 40 families with 118 children. The gene frequencies used for the calculations are taken from *Race* and *Sanger* (1954), except as regards the Lutheran system, where the frequencies calculated by *Mohr* (1951, b), Lu^a = 0.0428, Lu^b = 0.9572, are used.

Results

The results are presented in Table XIII. Both "certain" and "doubt-ful" families are scored, except as regards the MNS and Rh systems, which only include "certain" families. In each cell the upper number shows the linkage score, the middle number the total information, and the lower number shows the estimate of the linkage value 1—4 X, i.e. the linkage score divided by the information.

Out of the nine relations studied, cnly the one between AB0 and PTC shows a deviation in the direction of linkage. The deviation is however only significant at the $5°_0$ level, and there is no suggestion of it in other linkage data. It is therefore likely to be a chance deviation.

Table XIII. Linkage scores for PTC and the blood groups

	ABO	MNS	Rh	Le	Lu	P	Fy	K	Jk
	+ 7.09	− 6.48	+ 4.1	+ 2.15	− 0.49	− 3.54	− 0.41	+ 0.16	+ 2.39
PTC	13.4	19.0	27.3	3.0	2.8	2.6	7.4	0.8	10.6
	+ 0.49	− 0.34	+ 0.15	+ 0.7	− 0.17	− 1.36	− 0.05	+ 0.2	+ 0.22

Summary

Taste sensitivity to PTC has been determined in 266 unrelated Nor-wegian individuals by the sorting technique of *Harris* and *Kalmus*. The frequency of non-tasters was found to be 30.45%.

60 complete families with 176 children have been analysed with regard to the inheritance of the taste sensitivity to PTC. The data are in satis-factory agreement with the genetic hypothesis, that non-tasting is a simple recessive character.

A study of linkage relations between PTC and nine blood group systems is made on a material of 40 families with 118 children. No clear indication of linkage was found.

Zusammenfassung

Die Geschmacksempfindlichkeit auf PTC wurde bei 266 nicht mitein-ander verwandten Norwegern mit der Auswahl-Technik von Harris und Kalmus untersucht. Es fand sich eine Häufigkeit der Nichtschmecker von 30,45%.

60 vollständige Familien mit 176 Kindern wurden in bezug auf den Erb-gang der Geschmacksempfindlichkeit gegenüber PTC untersucht. Die Zahlen

stimmen befriedigend mit der genetischen Hypothese überein, daß Nicht-schmecken ein einfach-rezessives Merkmal ist.

An 40 Familien mit 118 Kindern wurden die Koppelungsbeziehungen zwischen PTC und 9 Blutgruppensystemen untersucht. Es zeigte sich kein deutlicher Hinweis auf Koppelung.

Résumé

L'épreuve gustative au PTC a été faite chez 266 individus norvégiens non apparentés, en se basant sur la technique de groupement indiquée par Harris et Kalmus. La fréquence des «non-tasters» a été de 30,45%.

60 familles avec 176 enfants ont été analysées en vue de l'hérédité de la faculté gustative au PTC. Les résultats correspondent avec l'hypothèse génétique que l'absence de cette faculté gustative est due à un facteur récessif simple. Une étude du linkage entre le PTC et 9 différents groupes sanguins a été faite chez 40 familles avec 118 enfants. Un linkage certain n'a pu être mis en évidence.

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INBREEDING IN A NORTH BELGIAN PROVINCE

By R. DERAEMAEKER, Antwerp

Information on the frequency of consanguineous marriages in human populations is said to be of value for estimating mutation rates (*Neel* [1952]), frequencies of recessive genes (*Lenz* [1919], *Weinberg* [1920], *Dahlberg* [1938], *Hogben* [1946], *Neel* et al. [1949] etc.) and sizes of isolates (*Dahlberg* [1929], 1938], *Morton* [1955], *Frotta-Pessoa* [1957]). It seems logical too, that any information on the breeding structure of a population will help to estimate how fast induced mutations will manifest themselves in homozygous condition.

Although the frequency of consanguineous marriages has been studied in several populations, it is clear that the information is still incomplete. As far as Belgium is concerned, I am not aware of any valuable information and although we may suppose that the consanguinity rate will be not very different from that found in similar West-European countries, we nevertheless found it interesting to examine the condition in some detail.

After some preliminary investigations, the study was actually started in 1955 and it went on for three years in the province of Antwerp.[1] This province, situated in the north of Belgium, covers an area of well over 2800 square km. with a population numbering 1 266 647 in 1947. From an administrative point of view the area is divided into three districts with a population number as given in table I.

Table 1. Area and population size in the districts of the province of Antwerp (1947)

District	Area in sq. km	Population Size	Number of individuals per sq. km
Antwerpen	1 000.72	775 586	783
Mechelen	503.56	247 262	494
Turnhout	1 356.17	243 799	183
Total	2 860.45	1 266 647	448

About 50 per cent of the total population live in urban areas; in the district of Antwerpen, which roughly covers the northwestern part of the province and includes the city of Antwerpen, the number reaches 66.8 per cent while in the Turnhout district, which covers the eastern part of the province, it is only 13.0 per cent. In the district of Mechelen, covering the southwestern and southern parts, the greater part of the population is rural but as the western part of the district is fairly heavily industrialized with many villages lying almost side by side, the urban conditions occur in a far greater area than that covered by the two towns, Mechelen and Lier.

Collection of Data

Lacking an official registration of consanguineous marriages, we have used parish records. These may be regarded as very important sources because the Roman Catholic Church permits marriages between relatives

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[1] Flemish names are used for districts and towns and the English manner of writing for the province.

up to second cousins only by special dispensation. The greater part of the
population being Roman Catholic, these records have undoubtedly fur-
nished information that for all practical purposes may be regarded as
representative for the whole of the population.[2] On the other side, as
marriages between second cousins once removed and above are not syste-
matically registered, we cannot be sure that the information on these types
is complete. Consequently we have decided not to use them in this study.

In all 164 629 marriages were investigated; 29 027 of these were con-
tracted during the period 1876–1900; 67 682 during the years 1901 to 1925
and 67 920 from 1926 to 1950 included.

The frequencies will be presented as percentages and use will be made of
the following abbreviations:

N = total number of marriages contracted during a given period.
1:2 = marriages between uncles and nieces and between aunts and
    nephews.
2:2 = marriages between first cousins.
2:3 = marriages between first cousins once removed.
3:3 = marriages between second cousins.
a = coefficient of inbreeding of the population for autosomal genes,
    calculated according to Haldane and Moshinsky (1939).

In the frequency data the cases of multiple consanguinity were dis-
regarded and marriages involving multiple degrees of consanguinity were
entered in the column of the closest degree involved if the degrees were
different.

The Data

(a) Trends in Time.

On the provincial level we observe a general tendency for decreasing
inbreeding rates (Table II). This tendency was most marked in the 1901 to
1925 period and seems less pronounced at this moment. On the district level

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[2] We do not know the percentage of Roman Catholics in the province but it is cer-
tainly not less than the percentage for the whole country which is about 95. If we accept
random mating we find that approximately 90 percent of all marriages are between Roman
Catholics, 9.5 per cent between a Roman Catholic and a non-Roman Catholic and about
0.25 per cent between non-Roman Catholics. As a great part of the marriages between a
Roman Catholic and a non-Roman Catholic are registered in the parish books, we may
accept that the parish records furnish information on approximately 95 per cent of all
marriages.

the observed tendencies are not uniform as the trends are not always the same in the rural and the urban parts (Table III). In the district of Antwerpen there is a general tendency for decreasing the inbreeding level in the urban areas but in the rural part the inbreeding rates give rather a picture of chance fluctuations. In the district of Mechelen the tendency to decrease the level seems quite general but in the district of Turnhout we observe a real "reversed" trend in the urban area while the rural part follows the more general tendency for decrease.

Table II. Inbreeding rates in the province of Antwerp

Period	N	1:2	2:2	2:3	3:3	α
1876–1900	29 027	0.096	0.451	0.203	0.671	0.000.57
1901–1925	67 682	0.050	0.415	0.104	0.387	0.000.41
1926–1950	67 920	0.051	0.356	0.069	0.400	0.000.37

(b) Trends in Space

Although we have not studied every parish or community in the province, our data show a rather definite trend in space. In the last period
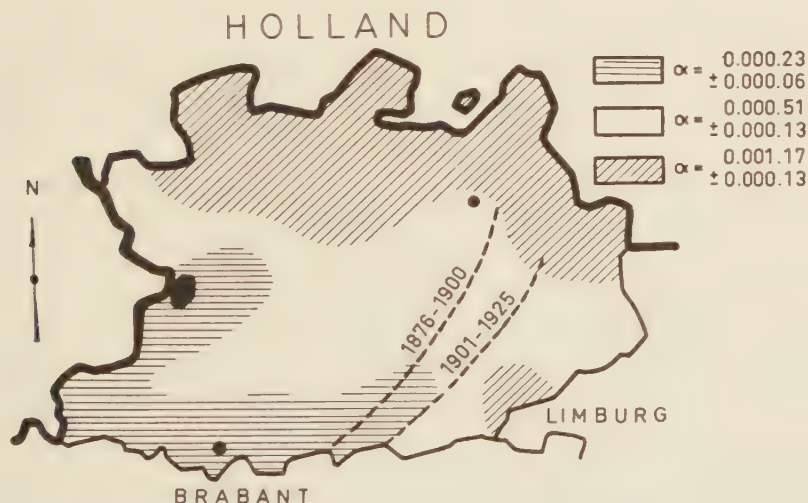
Fig. 1. Trends in space in the province of Antwerp

1876–1900: Mean and higher than 0.001.00 east of this
1901–1925: border in the period 1876–1900 resp. 1901–1925

Table III. Inbreeding in the districts of the province of Antwerp

District Antwerpen

Period	N	1:2	2:2	2:3	3:3	α
(a) urban part (= city of Antwerpen + suburbs)						
1876–1900	11 346	0.176	0.405	0.132	0.290	0.000.55
1901–1925	37 746	0.069	0.421	0.055	0.196	0.000.39
1926–1950	38 145	0.049	0.325	0.034	0.131	0.000.29
(b) rural part						
1876–1900	5 998	0.033	0.346	0.346	0.808	0.000.49
1901–1925	9 074	0.044	0.473	0.198	0.616	0.000.53
1926–1950	9 991	0.080	0.400	0.110	0.710	0.000.49

District Mechelen

Period	N	1:2	2:2	2:3	3:3	α
(a) urban part (= towns of Mechelen and Lier)						
1876–1900	2 152	0.000	0.325	0.000	0.511	0.000.28
1901–1925	4 739	0.000	0.295	0.063	0.189	0.000.23
1926–1950	3 675	0.000	0.217	0.000	0.027	0.000.14
(b) rural part						
1876–1900	3 724	0.053	0.583	0.106	0.715	0.000.58
1901–1925	5 401	0.000	0.274	0.146	0.695	0.000.33
1926–1950	6 094	0.016	0 262	0.096	0.464	0.000.28

District Turnhout

Period	N	1:2	2:2	2:3	3:3	α
(a) urban part (= town of Turnhout)						
1876–1900	2 783	0.107	0.035	0.070	0.140	0.000.20
1901–1925	2 659	0.146	0.150	0.146	0.146	0.000.28
1926–1950	2 465	0.160	0.243	0.040	0.324	0.000.42
(b) rural part						
1876–1900	3 024	0.033	1.122	0.561	2.343	0.001.28
1901–1925	4 963	0.020	0.924	0.301	1.648	0.000.95
1926–1950	7 550	0.039	0.633	0.211	1.399	0.000.94

(1926–1950) the lowest coefficients of inbreeding occur in and around the city of Antwerpen and in the south and south-western part of the province. The mean coefficient of inbreeding for that area is 0.000.23 ± 0.000.06. The highest coefficients are observed in the most northern and north-eastern parts and in some localities in the south-east of the province. The mean coefficient of inbreeding is 0.001.17 ± 0.000.13. In between lies an area with a mean coefficient of inbreeding of 0.000.51 ± 0.000.13.

This trend is also obvious in the other periods and it is most remarkable that the border of the region with the highest coefficients of inbreeding has gradually shifted to the east and has actually crossed the eastern border of the province. At this moment the highest coefficients are found, as said, in the north of the province and in some parts of the south-east while about 40–50 years ago the whole eastern part showed the highest coefficients in the province (fig. I).

The shifting of the above mentioned border has created in the eastern part of the province a region with coefficients of inbreeding which are still high but intermediate between the region with low coefficients in the south and the area with high inbreeding in the north. The result of this situation is a tendency to form gradients which have their origin in the south and south-south-west and run north and north-north-east.

(c) Nature of the relationship of first cousins.

It is obvious that first cousins can be related to one another in four possible ways as depicted in fig. II.

Type I   Type II   Type III   Type IV
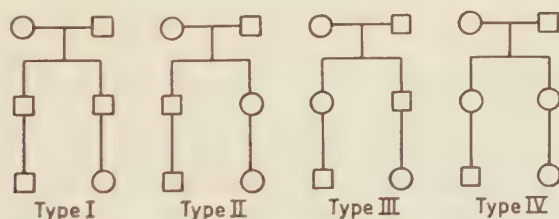
Fig. 2. Different types of marriages between first cousins.

In a sample of 242 marriages between first cousins the following proportions were observed: type I, 27.69 per cent; type II, 22.73 per cent; type III, 26.03 per cent and type IV, 23.15 per cent. These frequencies do not deviate from the expected 25 per cent on the hypothesis of randomness.

Discussion

Undoubtedly there are many factors which account for the differences in inbreeding rates and it seems very difficult to evaluate the specific part of each of them in the process. The demographic density is one of the factors which is most easily analysed. Although there is generally a negative correlation between the coefficient of inbreeding and the population density (graph. I), a more detailed analysis shows that for the same density socio-economic factors play an important part. These socio-economic factors are reflected in the reversed trends observed in some areas of the province. In one of these areas an analysis made it clear that the kind of occupation coupled to the practice of marrying someone of the village had increased the inbreeding in recent times while in the neighbouring areas where these factors did not play so great a role, a decrease was very obvious.
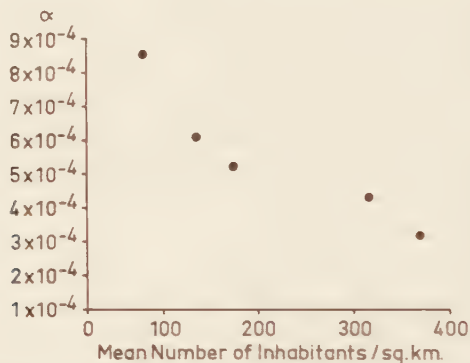
Graph I. Negative correlation between coefficient of inbreeding and population density.

Several investigators (*Orel* [1932], *Morton* [1955], *Shields* and *Slater* [1956], and *Nixon* and *Slater* [1957]) have found that in the marriages between first cousins, type IV is more common than the other types. Shields and Slater explain this by the fact that in this form of cousin-marriages the common grand parental surname is most hidden. They also propose a social reason viz. that the children of two sisters have a greater chance of meeting one another than the children of two brothers and of a brother and a sister.

In the province of Antwerp type I is slightly more frequent (27.69 per cent) than type IV (23.15 per cent) but if we push the analysis a little further we observe that in urban areas type IV is far more common than type I, while the reverse is true in the rural areas (Table IV). This seems to

indicate that in urban areas people try to conceal the consanguineous character of some marriages while in rural parts they do not. It might be that this has something to do with the higher educational level in urban areas.

Table IV. Types of first cousin marriages in urban und rural areas

Type	I	II	III	IV
urban areas	14.3	35.6	14.3	35.6
rural areas	29.2	21.3	28.0	21.3

Conclusion

The data show that inbreeding in the province of Antwerp follows the same general pattern as that commonly found in other West-European countries in which the same geographical situations occur. In urban areas inbreeding is lower than in rural parts and in general the rate of consanguinity was higher some generations ago than it is at this moment. Reversed trends, sporadically observed, seem connected with special socio-economic factors; this is obvious in some localities and may be of general occurrence.

Our data do not quite agree with the statement of several authors that in marriages between first cousins, type IV occurs more frequently than the other types. The urban areas of the province of Antwerp agree well with what these authors found but in rural areas type I is more common than type IV.

Summary

The results of a study on consanguinity in the province of Antwerp are presented. These show a steady decline in time when the province is taken as a whole but the tendency is not uniformly observed all over the province. Trends in space have also been observed but the statement of several authors that among marriages between first cousins type IV is more common than the other types, could be confirmed for urban areas only, not for the rural part of the province.

Zusammenfassung

Es werden die Ergebnisse einer Untersuchung über Blutsverwandtenehen in der Provinz Antwerpen vorgelegt. Die Häufigkeit solcher Ehen zeigt einen stetigen Abfall in der Zeit, wenn man die Provinz als ganze

betrachtet. Jedoch beobachtet man diese Tendenz nicht gleichmäßig in allen ihren Teilen. Es gibt auch räumliche Unterschiede. Die Feststellung mehrerer Autoren, daß unter den Vetternehen 1. Grades der Typ IV häufiger sei als die anderen Typen, ließ sich nur für die Städte, nicht aber für den ländlichen Teil der Provinz bestätigen.

Resumé

L'auteur a fait des recherches au sujet de la fréquence de la consanguinité dans la province d'Anvers. On constate une diminution constante avec le temps si la province est prise en totalité, mais cette tendance ne s'étend pas à toute la province. Si l'on constate une certaine tendance uniforme dans certaines régions, les constatations de plusieurs auteurs que parmi les mariages entre cousins germains le type IV (les mères étant sœurs) est plus fréquent que les trois autres types ont pu être confirmées pour des régions urbaines, mais pas pour les parties rurales de la province.

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BLOOD GROUPS AND ANTHROPOLOGY
IN DALECARLIA (SWEDEN)

By LARS BECKMAN and ERIK H. MÅRTENSSON

Because of the interesting physical anthropological conditions in the Swedish province of Dalecarlia the authors decided to carry out a blood group genetical study of the province. The material is blood group determinations on conscripts collected by *Beckman* and data from a blood donor campaign under the sponsorship of The Swedish Red Cross led by *Mårtensson*.

Earlier anthropological investigations

The Swedish province Dalecarlia has since long ago been considered to contain an anthropologically interesting population. The term "the Dalecarlian type" was first introduced in 1874 by the anthropologists *Quatrefages* and *Hamy* (cf. *Lundman* 1952). *Paudler* (1917–18 and 1924) claimed to have established the occurrence of a fair Cro-Magnid population with its centre in Dalecarlia in Sweden, and a dark Cro-Magnid population on the Iberian paeninsula and among the Berbers of north Africa. *Lundborg* and *Linders* (1926) dispatched the Cro-Magnon like elements in Dalecarlia as a type whose heredity has not been demonstrated and which may probably be interpreted as a mixture of Nordic and East Baltic races. *Backman* (1927) objects to this, and declares that no reason exists for assuming a Nordic-East Baltic mixture, but that the type may be quite simply an extreme variant of the Nordic Race. Data from "The Racial Characters..." (1926) show however that the frequency of purer East Baltic types is lowest in central Sweden and Dalecarlia where the particular Dalecarlian type is said to be found. *Lundman* has treated the anthropogeographical problems

of Dalecarlia in several works (e.g. 1945, 1946, and 1952). In his dissertation he studied the local types and arrived at the conclusion that the primary groups distinguishable in the province represent important main categories in the regional anthropology of Scandinavia. *Lundman* points to the dark, broad-faced, tall and dolichocephalic element in the forest villages of northwestern Dalecarlia as the oldest element. This type – the Tydal type – is according to *Lundman* Cro-Magnon like and occurs in several mutually disconnected areas in the interior of the Scandinavian peninsula. Related types are said to exist in the mountainous districts of the British Isles, as well as here and there in western Europe as far south as the Canary Islands. The next oldest element is according to *Lundman* a short, broad-faced dolichocephalic and fair type occurring in the central parts of Dalecarlia.

The Finnish influence in Dalecarlia is according to *Lundman* very slight, while intermixing with gipsies should be more clearly detectable. However, there is historical evidence for a considerable Finnish immigration to Dalecarlia during the sixteenth and seventeenth centuries.

Earlier known blood group data

Data as to variation of AB0- and Rh-blood groups in Sweden up to 1954 have been summarized by *Mourant* (1954). The only series previously published from Dalecarlia is as far as we know a series by *Grubb* and *Wiklund* (1953). The sample comprised 600 individuals and gave the following gene frequencies:

A	B	0
28.45	7.47	64.08

Our blood group data

A. The conscript material

The material has been obtained from the infantry regiment at Falun (1:13).

Regional classification:

Region	Parishes
1	Idre and Särna
2	Transtrand and Lima
3	Älvdalen
4	Mora, Våmhus, and Sollerön

Region	Parishes
5	Malung and Venjan
6	Orsa
7	Ore
8	Rättvik and Boda
9	Siljansnäs and Leksand (without Djura)
10	Järna and Äppelbo
11	Nås, Floda, Säfsnäs, and Mockfjärd
12	Grangärde and Ludvika rural community
13	Norrbärke
14	Söderbärke and Malingsbo
15	Ål and Bjursås
16	Gagnef and Djura (a part of Leksand)
17	Stora Tuna
18	Falu rural community, Aspeboda, Vika, and Torsång
19	Sundborn, Svärdsjö, and Enviken
20	Stora Skedvi and Säters rural community
21	Husby
22	Hedemora rural community, Folkärna, By, Garpenberg, and Grytnäs
23	Gustavs and Silvberg

Densely populated eastern Dalecarlia has been divided into fairly small areas. Those in the northwest are larger because of larger parishes, and the data for certain parishes have been considered together.

The consistency with the expected frequencies is satisfactory for the total material, but two of the constituent areas show inconsistency.

A significant heterogeneity exists for A+AB ($\chi^2 = 62.58$, 22 d. f., P < 0.001). The average, 28.3 per cent, agrees with *Mourant*'s earlier mapping. Frequencies vary from 24.1 per cent in subregion 23 to 37.1 per cent in subregion 5. Apart from this aforementioned maximum in subregion 5 (in the southwestern part of the province), frequencies above 30 per cent are found only in the east, in subregions 18, 19, and 20.

The B+AB frequency also shows a significant heterogeneity ($\chi^2=87.66$, 22 d. f., P<0.001), with a relatively high average (8.3 per cent). Six regions exhibit frequencies above 10 per cent. The highest frequency, 13.2 per cent, in subregion 11, corresponds to the values found in Finland. Low values, down to 5–6 per cent, are encountered both in the northwest and the east. Map 1 shows a northsouth stretch of high B-values dividing Dalecarlia into two areas of lower B-frequencies.

Dalecarlia's high B-frequencies must be considered indicative of the presence of eastern elements. It is rather tempting to assume that the high frequencies become concentrated in areas where the Finnish immigration

Table 1

Subregions	A	B	AB	0	n	χ^2	p	q	r	p+q+r
1	108	21	9	98	236	1.06	29.1	5.9	65.0	99.24
2	119	28	2	104	253	3.40	29.0	5.8	65.2	98·70
3	166	42	12	191	411	4.65	25.1	5.9	69.0	98.91
4	283	96	35	312	726	0.13	25.1	9.6	65.3	100.18
5	257	50	23	135	465	1.64	37.1	8.3	54.6	99.03
6	169	60	18	129	376	2.39	29.4	11.0	59.6	98.72
7	63	24	9	68	164	0.01	25.1	10.6	64.3	100.12
8	147	44	12	152	355	0.87	25.8	8.3	65.9	99.38
9	187	43	12	201	443	0.72	25.8	6.4	67.8	99.56
10	162	51	31	135	379	1.88	29.8	11.5	58.7	101.17
11	137	58	22	111	328	0.27	28.3	13.2	58.5	99.50
12	88	26	11	79	204	0.002	28.3	9.5	62.2	100.04
13	145	41	20	138	344	0.37	27.8	9.3	62.9	100.46
14	57	25	7	60	149	0.27	24.6	11.5	63.9	99.38
15	110	19	11	107	247	0.60	28.4	6.3	65.3	100.57
16	101	24	7	110	242	0.26	25.6	6.6	67.8	99.64
17	458	107	44	388	997	0.04	29.6	8.0	62.4	99.92
18	126	14	14	101	255	3.54	32.6	5.6	61.8	101.41
19	183	38	15	142	378	0.15	31.1	7.5	61.4	99.73
20	146	35	7	117	305	0.003	31.8	9.0	59.2	100.05
21	97	21	9	94	221	4.95	29.4	6.9	63.7	101.86
22	138	24	12	138	312	0.54	27.9	6.0	66.1	100.46
23	56	27	13	66	162	1.17	24.1	13.2	62.7	101.32
Total	3503	918	355	3176	7952	1.78	28.3	8.3	63.4	99.80

during the seventeenth century is known to have been considerable. A rough calculation shows that an immigrating eastern population with, let us say, 14 per cent of gene B must have formed about 40 per cent of the final mixed population, in order to raise the B-frequency from 7 to 10 per cent. This calculation has been based on a 10 per cent B-frequency in central Dalecarlia. If the observed B-frequencies (up to 12–13 per cent) in Dalecarlia are significant and not mere chance, the eastern intermixture will be still greater. According to *Hülphers* (1763), the number of Finnish households during the eighteenth century seldom exceeded 10 per cent in every parish. Thus, there may be causes for this frequency increase antecedent to the Finnish immigration in the seventeenth century, though the latter factor cannot be discredited. *B. Lundman* (1945) says that the region in southwestern Dalecarlia where the B-frequency is high must be considered as very "Nordic".

Map 1

Map 2

Map 1

1
29.1
5.9
65.0

3
25.1
5.9
69.0

2
29.0
5.8
65.2

6
29.4
11.0
59.6

7
25.1
10.6
64.3

4
25.1
9.6
65.3

8
25.8
8.3
65.9

5
37.1
8.3
54.6

9
25.8
6.4
67.8

15
28.4
6.3
65.3

19
31.1
7.5
61.4

10
29.8
11.5
58.7

16
25.6
6.6
67.8

18
32.6
5.6
61.8

17
29.6
8.0
62.4

21
29.4
6.9
63.7

20
31.8
9.0
59.2

11
28.3
13.2
58.5

12
28.3
9.5
62.2

23
24.1
62.7

13
27.8
9.3
62.9

14
24.6
11.5
63.9

22
27.9
6.0
66.1

Map 2

1
30.7
9.5
59.8
14.7

3
26.3
9.8
63.9
10.3

2
35.0
10.2
54.8
11.7

6
31.3
10.7
58.0
9.6

7
31.9
8.3
59.8
11.2

4
24.7
12.5
62.8
13.8

8
26.3
8.1
65.6
14.2

5
30.6
11.0
58.4
18.8

9
29.9
6.0
64.1
13.4

10
29.9
10.9
59.2
13.8

19
29.6
7.9
62.5
9.8

15
29.3
15.1

16
24.9
10.5
64.6
11.3

18
32.1
8.6
59.3
15.1

17
31.4
7.3
61.3
13.4

20
30.5
6.1
63.4
29.8
61.9
14.4

21
12.7

11
27.9
10.5
61.6
15.5

12
30.5
9.4
60.1
15.1

13/14
28.6
8.4
63.0
15.3

22
8.3

23
26.0
6.4
67.6

14.0

Map 1
The conscript material. A-, B- and 0-frequencies.

Map 2
The blood donor material. A-, B- and 0-frequencies and D-negatives (underlined figures).

Significant heterogeneity exists for the frequency of the 0-group ($\chi^2 =$ 291.02, 22 d.f., P $<$ 0.001). Subregion 3 shows a maximum value of 69 per cent. Values above 65 per cent occur in the regions around Lake Siljan and the river Österdalälven, and in a smaller area in the southeast. According to *Mourant*'s map, no area in Sweden should exhibit a frequency above 65 per cent. The mean value for the entire province is 63,4 per cent. Southwestern Dalecarlia, a separate region in which the low values are concentrated, is pointed out by *Lundman* as a region inhabited mainly by "Göta types". This does not agree with the idea that the southwest Swedish Göta type ought to have rather high 0-frequencies. Since, at the same time, B-frequencies in this area are high, the AB0-data ought rather to be considered as pointing to an eastern influence.

B. The Blood donor material

Blood group determinations were made under Dr. *Mårtensson*'s supervision at the Blood Donor Central of the Falu Hospital. The campaign was

very extensive, with blood group analyses for 10.719 individuals. First analysis showed a strongly pronounced inconsistency with the expected frequencies ($\chi^2 = 13.74$, 1 d.f., $0.001 > P$). The following table contains the observed and the expected frequencies.

<div align="center">Table 2</div>

	A	B	AB	0	n	χ^2	p+q+r
Observed	4791	1172	627	4129	10,719	13.74	100.51
Expected	4848.1	1245.1	558.4	4067.4	10,719		

We notice a considerable excess of AB- and 0-individuals. and a corresponding deficiency of A- and B-individuals. This type of inconsistency, implying an excess of AB, is relatively unusual. The most common feature is a deficiency of AB-individuals. The excess of AB is compensated by deficiencies of both B and A. Consequently, the calculation of genes A and B is influenced only in a relatively small degree. The frequency of gene 0 becomes, however, evidently too high. Two of the part series (Grytnäs and the town of Avesta, and Gustavs) could be seen immediately, without any calculation, to have abnormally high AB-frequencies. They were excluded from the total material pending further examination. The remaining material included data for 9966 individuals.

This was classified into 21 part regions, corresponding generally to the classification of the conscript material.

a) The AB0-system

In spite of the removal of inconsistent samples, there still remains a significant inconsistency with the expected frequencies for the total material ($\chi^2 = 7.88$, 1 d.f., $0.01 > P > 0.001$). Only one of the constituent areas, subregion 12 shows a significant inconsistency. If this region is omitted, we obtain $\chi^2 = 3.21$, 1 d.f., $0.1 > P > 0.05$ for the rest of the material.

The difference for the frequency A + AB between this material and the conscript material gave $\chi^2 = 6.87$, 1 d.f., $0.01 > P > 0.001$. Thus, the A-frequency is higher and the 0-frequency lower in this material, and the difference is significant. The difference for the frequency B + AB between the two materials gave $\chi^2 = 1.99$, 1 d.f., $0.2 > P > 0.1$. No established difference is seen here.

The variation of the frequencies A+AB between the different part regions gave $\chi^2 = 33.43$, 20 d.f., $0.05 > P > 0.02$. The variation of the fre-

quencies B+AB gave $\chi^2 = 215.43$, 20 d.f., $0.001 > P$. In the conscript material the levels of significance were $0.01 > P > 0.001$ and $0.001 > P$, respectively. Thus, in either case, the gene B exhibited greater heterogeneity.

A comparison between this map and the one for the conscript material shows main-line agreement. The B-frequencies are fairly high in central

Table 3

Parishes or towns	A	B	AB	0	n	χ^2	p	q	r	p+q+r
1. Idre, Särna	58	17	5	42	122	0.61	30.7	9.5	59.8	98.60
2. Transtrand, Lima .	37	7	8	25	77	1.60	35.0	10.2	54.8	102.79
3. Älvdalen	107	33	18	114	272	1.67	26.3	9.8	63.9	101.09
4. Mora, Våmhus, Sollerön	112	53	16	115	296	0.41	24.7	12.5	62.8	99.43
5. Malung, Venjan . .	115	36	17	87	255	0.001	30.6	11.0	58.4	99.96
6. Orsa	260	74	42	195	571	0.61	31.3	10.7	58.0	100.54
7. Ore	80	16	11	62	169	0.73	31.9	8.3	59.8	100.96
8. Rättvik, Boda . .	81	19	13	91	204	2.84	26.3	8.1	65.6	101.48
9. Siljansnäs, Leksand o. Djura	52	8	5	47	112	0.43	29.9	6.0	64.1	100.72
10. Järna, Äppelbo . .	148	47	22	117	334	0.002	29.9	10.9	59.2	100.04
11. Nås, Floda	84	28	12	76	200	0.007	27.9	10.5	61.6	100.09
12. Grangärde, Gränges-berg, Ludvika stad o. landsk.	535	127	89	449	1200	9.33	30.5	9.4	60.1	101.33
13.,14. Norrbärke, Smedjebacken, Söderbärke, Malingsbo	218	54	29	201	502	0.32	28.6	8.4	63.0	100.34
15.,16. Gagnef, Mock-fjärd, Åhl, Bjursås .	136	52	18	147	353	0.009	24.9	10.5	64.6	99.93
17. St.Tuna	888	204	98	780	1970	0.74	29.3	8.0	62.7	100.26
18. St. Kopparberg, Falun, Vika . . .	511	114	61	374	1060	0.08	32.1	8.6	59.3	100.13
19. Sundborn, Svärdsjö, Enviken	119	28	14	103	264	0.02	29.6	7.9	62.5	99.88
20. St.Skedvi, Säter o. Säters landsk. . .	227	44	22	177	470	0.03	31.4	7.3	61.3	100.10
21. Husby	144	25	10	119	298	0.12	30.5	6.1	63.4	99.76
22. Hedemora stad o. landsk., Folkärna o. Krylbo köp. . . .	399	96	44	334	873	0.004	29.8	8.3	61.9	100.03
23. By	150	29	16	169	364	1.75	26.0	6.4	67.6	100.77
Total	4461	1111	570	3824	9966	7.88	29.6	8.8	61.6	100.40

Dalecarlia. but decrease toward the east. This material confirms higher than 10 per cent B-frequencies throughout large parts of Dalecarlia. In the conscript material the subregions 1–3 exhibited low and uniform frequencies (5.8–5.9 per cent). while in the blood donor material their frequencies are high and equally even (9.8–10.2 per cent). The difference is significant. The reason may be that the conscript material which has been arranged according to the parishes of birth. may perhaps be a more representative sample. Certainly the blood donor material comes mostly from those easily accessible. densely populated places whose populations are infused with the high B-frequency element of central Dalecarlia. Persons from out-of-the-way regions have been included to a comparatively small extent.

In either material the highest A-frequencies are found in the west. and in either material subregions 3. 4. 8. 15. and 16 show low A-frequencies.

The heterogeneity for the frequency of the 0-group gives $\chi^2 = 35.58$. 20 d.f.. $0.02 > P > 0.01$. On account of discrepancies seen in the 0-group. nothing definite can be said about the significance of the variation.

The 0-values are higher in the conscript material than in this. In both records the subregions 3. 4. 5. 9. 15. and 16 exhibit relatively high 0-frequencies.

b) The Rh-system

Frequencies in the different part regions can be seen in table 4.

The total material exhibits a relatively low frequency. i.e. 13.97 per cent. of D-negative individuals. No significant heterogeneity exists for the frequency of D-negative individuals ($\chi^2 = 28.77$. 20 d.f.. $0.1 > P > 0.05$). In map 2 the frequency of D-negative individuals is found below the ABO-figures (underlined figures). The maximum. 18.8 per cent. is found in subregion 5: the minimum. 9.6 per cent. in subregion 6. The difference between subregion 5 and the remaining subregions corresponds to $\chi^2 = 4.76$. 1 d.f.. $0.5 > P > 0.02$. The increase of frequency in southern Dalecarlia as a whole is not significant. No direct agreement with the variation for the ABO-genes can be established. The relatively low frequencies for D-negative individuals may depend upon eastern elements. since eastern populations exhibit relatively low frequencies of D-negative individuals.

Discussion

The inconsistency revealed by the blood donor material may possibly be explained as a selection depending on the fact that men often remember their blood group from their military service. They may also know that AB

Table 4

No.	D+	%	D–	%	n	D gen	d gen
1	104	85.3	18	14.7	122	61.6	38.4
2	68	88.3	9	11.7	77	65.9	34.1
3	244	89.7	28	10.3	272	67.9	32.1
4	255	86.2	41	13.8	296	62.8	37.2
5	207	81.2	48	18.8	255	56.6	43.4
6	516	90.4	55	9.6	571	69.0	31.0
7	150	88.8	19	11.2	169	66.5	33.5
8	175	85.8	29	14.2	204	62.3	37.7
9	97	86.6	15	13.4	112	63.4	36.6
10	288	86.2	46	13.8	334	62.9	37.1
11	169	84.5	31	15.5	200	60.6	39.4
12	1019	84.9	181	15.1	1200	61.2	38.8
13,14	425	84.7	77	15.3	502	60.8	39.2
15,16	313	88.7	40	11.3	353	66.3	33.7
17	1679	85.2	291	14.8	1970	61.6	38.4
18	900	84.9	160	15.1	1060	61.1	38.9
19	238	90.2	26	9.8	264	68.6	31.4
20	407	86.6	63	13.4	470	63.4	36.6
21	260	87.3	38	12.7	298	64.3	35.7
22	747	85.6	126	14.4	873	62.0	38.0
23	313	86.0	51	14.0	364	62.6	37.4
Total	8574	86.03	1392	13.97	9966	62.62	37.38

is rare and 0 is a "good group" and thus enroll themselves more often as blood donors as do A- and B-individuals.

In spite of the inconsistency shown by the blood donor material some reliable main traits of variation can be traced. The most reliable heterogeneity is shown by the B-frequency. The relatively high B-frequencies in some areas of Dalecarlia probably depend on an eastern influence. No B-frequencies above 10 per cent have earlier been reported from Sweden, but in Dalecarlia vast areas have frequencies above 10 per cent. The eastern influence is surely partly due to the Finnish immigrations during the sixteenth and seventeenth centuries, but still older eastern immigrations may have contributed.

Because of the discrepancies connected with the A- and 0-groups one should be careful when drawing conclusions as to the statistical significance of the variation here. Possibly, however, the relatively high 0-frequencies may be looked upon as indicative of a west European influence.

The relatively low frequencies of D-negative individuals also point to an eastern influence in Dalecarlia.

Summary

1. AB0-data are given for 7592 conscripts and 9966 blood donors.

2. Rh-data are given for 9966 blood donors.

3. The consistency with expected frequencies is more satisfactory concerning the conscript material which shows the usual slight deficiency of AB. The blood donor material reveals an unusual discrepancy consisting of an excess of AB and 0.

4. Significant regional heterogeneity has been established for the A-, B- and 0-genes but not for the frequency of D-negatives.

5. The high B-frequencies in Dalecarlia seem to agree with historically known immigrations from the east.

Zusammenfassung

1. AB0-Daten werden angegeben für 7592 Rekruten und 9966 Blutspender.

2. Rh-Daten werden für 9966 Blutspender mitgeteilt.

3. Die Übereinstimmung mit den erwarteten Häufigkeiten ist bei den Rekruten besser; hier findet man die übliche leichte Verminderung von AB. Bei den Blutspendern zeigt sich eine ungewöhnliche Diskrepanz, da AB und 0 zu stark vertreten sind.

4. Eine signifikante regionale Heterogenität wurde für die A-, B- und 0-Gene, nicht jedoch für die Häufigkeit der Rh-Negativen festgestellt.

5. Die große B-Häufigkeit in Dalecarlia entspricht offenbar den aus der Geschichte bekannten Einwanderungen aus dem Osten.

Resumé

1. La fréquence des groupes sanguins AB0 chez 7592 recrues et 9966 donneurs de sang est donnée.

2. Pour les donneurs, les groupes Rh sont également indiqués.

3. Pour les recrues, les données statistiques correspondent assez bien aux chiffres théoriques. Comme d'habitude, le chiffre pour le groupe AB est un peu bas. Chez les donneurs, on a trouvé un excès inhabituel des groupes AB et 0.

4. Une différence régionale significative a été calculée pour les groupes AB et 0, mais pas pour le groupe Rh négatif.

5. La fréquence relativement haute du groupe B en Dalecarlia semble être en rapport avec l'immigration historiquement connue venant de l'est.

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A SIMPLE METHOD OF MATCHING CERTAIN RESULTS FROM INVESTIGATIONS OF UNIOVULAR TWIN PARTNERS

By N. JUEL-NIELSEN and ARNE NIELSEN

In connection with a psychiatric-psychological investigation of a limited series of uniovular twins who had grown up apart in childhood, attempts were made to evaluate certain psychological tests and the results of other special investigations by means of a simple method of matching which does not appear to have been previously submitted to theoretical analysis. Results of investigations are concerned which cannot be exhaustively described or classified numerically.

The results of the electroencephalographic investigation in the material will be mentioned to illustrate the method employed and the problems associated with it.

The material comprizes 8 uniovular pairs of twins. With this material the following experiment was carried out: Representative pieces of the 16 EEGs were mixed and thereafter placed in random order, unknown to an outsider. Two physicians without special knowledge of EEG were then requested to pair the EEGs correctly. Both physicians were able to do this successfully: solely on a basis of the immediate similarity between the curves it was possible to reunite all the pairs of twins correctly.

In evaluating the results obtained in the method of matching described, the following question arises: how great is the probability of matching a given number of pairs correctly by chance alone?

If the number of correctly matched pairs found deviated significantly from the number which might be anticipated the result would support the presumption that genetic factors play a part concerning the function investigated. Presuming that other factors such as age and sex do not play any part, the result must be interpreted as an expression that variations concerning the function involved are considerably less between the partners in pairs of uniovular twins than between unrelated individuals. e.g. all twin partners in the random series.

Recently, *Vogel* (1957) on the basis of EEGs from a more extensive material of uniovular pairs of twins undertook an identification experiment which demonstrates convincingly that the intuitive general impression grasps a similarity which by far exceeds that which can be measured. The procedure in the method employed by *Vogel* deviates in principle from that described by the authors of the present paper as *Vogel* determined in advance the one series of partners while we undertook matching among all the results of the investigation placed in an unknown and random order. The latter method involves a considerably greater comparative work but appears appropriate, when twin materials are concerned which must necessarily be limited for one reason or other. The advantages of the method in respect of statistics will be accounted for below. Mention will first be made of the mathematical-statistical considerations to which the method and the question have given rise.

Mathematical-statistical account (A.N.)

In calculating the probability of matching v pairs of n pairs correctly in a random manner, it is presumed that matching is carried out by mixing the $2n$ results so that these come to rest in random order. The 2 first in the

series thus constitute a matched pair, similarly the next 2 and so on until the last 2 constitute the last matched pair.

The 2n results may with this procedure be laid up in (2n)! different ways. The number of these which implies that exactly ν pairs are correctly matched is called k(ν/n).

It is then found directly that

$$k(n/n) = n!\, 2^n, \tag{1}$$

as the n correctly matched pairs may be laid in series in n! different ways and the 2 individuals in a pair may be placed in 2 different ways within the pair.

In addition it appears immediately that

$$k(n{-}1/n) = o. \tag{2}$$

For the ordinary link the recursion equation is available

$$k(\nu/n) = \binom{n}{\nu} n^{(\nu)} 2^\nu k(o/n{-}\nu)$$

$$= \binom{n}{\nu} k\,(n/n)\, \frac{k\,(o/n{-}\nu)}{-k\,(n{-}\nu/n{-}\nu)}, \quad (o < \nu \leqq 2) \tag{3}$$

in which $n^{(\nu)}$ indicates the product $n(n{-}1)(n{-}2)\ldots(n{-}\nu{+}1)$. The correctness of the equation appears from the first line in equation (3). The ν correctly matched pairs of twins may be taken in $\binom{n}{\nu}$ ways from the total number of twins pairs n. These ν correctly matched pairs may be placed in $n^{(\nu)}$ ways in the series. The first pair may be placed in n ways. When the first pair has been placed, the next may be placed in n—1 different ways etc. until the νth. pair may be placed in n—ν+1 different ways. The two partners in each pair may be placed in two different ways within the pair. Out of the remaining n—ν pairs of twins none will be correctly matched and the number of ways in which this can be done is called k(o/n—ν). If k(o/n—ν) is known, k(ν/n) may be calculated.

When k(ν/n) has been calculated for ν = 1, 2 .... n, k(o/n) may be calculated using the equation

$$k(o/n) = (2n)!{-}k(1/n){-}k(2/n){-}\ldots{-}k(n/n). \tag{4}$$

The probability of matching correctly ν pairs out of n pairs of twins at random is found by the factor k(νn)/(2n)!. In *Table 1* these factors are given for n = 1, 2, ..., 12. It can be demonstrated that when n approaches infinity the distribution in the limit will be a Poisson distribution with the mean value $\frac{1}{2}$. The probabilities of this distribution are also recorded in Table 1.

The agreement of the formula with practice was investigated in the following manner:

Fisher and *Yates* (1957) recorded 200 random permutations of the numbers from 0 to 19. We have employed numbers which ended with the same figure such as 0 and 10, 1 and 11, 2 and 12 etc. as natural pairs, a total of 10 pairs. The numbers opposite one another in the first and second and

Table 1. The probability of matching correctly v pairs by random permutation
of 2n paired individuals.

Number of pairs	Number of correctly matched pairs, v								
n	0	1	2	3	4	5	6	7	Total
1	0	1							1
2	0.6667	0	0.3333						1.0000
3	0.5333	0.4000	0	0.0667					1.0000
4	0.5714	0.3048	0.1143	0	0.0095				1.0000
5	0.5757	0.3175	0.0847	0.0212	0	0.0011			1.0002
6	0.5810	0.3140	0.0866	0.0154	0.0029	0	0.0001		1.0000
7	0.5847	0.3129	0.0845	0.0155	0.0021	0.0003	0	0.0000	1.0000
8	0.5874	0.3118	0.0834	0.0150	0.0021	0.0002	0.0000	0	0.9999
9	0.5895	0.3110	0.0825	0.0147	0.0020	0.0002	0.0000	0.0000	0.9999
10	0.5912	0.3103	0.0818	0.0145	0.0019	0.0002	0.0000	0.0000	0.9999
11	0.5926	0.3097	0.0813	0.0143	0.0019	0.0002	0.0000	0.0000	1.0000
12	0.5938	0.3092	0.0808	0.0141	0.0019	0.0002	0.0000	0.0000	1.0000
	Poisson distribution with the mean value								
½	0.6065	0.3033	0.0758	0.0126	0.0016	0.0002	0.0000	0.0000	1.0000
1	0.3679	0.3679	0.1839	0.0613	0.0153	0.0031	0.0005	0.0001	1.0000

in the third and fourth lines of the group were employed as randomly
matched pairs. The number of correctly matched pairs was then added up
for each of the 200 permutations.

In *Table 2* in the column "Observed" is recorded how the 200 per-
mutations were distributed according to the number of correctly matched
pairs. In the column "Calculated" is recorded how many pairs would be
anticipated according to Table 1 for n = 10. It will be observed that the
agreement is good.

Table 2.   Observed and calculated number of correctly matched pairs in 200 permutations
of 20 paired individuals.

Number of correctly matched pairs	Number of permutations	
	Observed	Calculated
0	123	118.2
1	60	62.1
2	15	16.4
3	2	2.9
4	0	0.4
Total	200	200.0

Feller (1950) has given equations for the probability of matching v pairs out of n pairs of twins correctly when the one series of partners has been determined in advance. This is the basis for the method employed by *Vogel*. In the same connection, *Feller* has provided a table for some values for n. It appears that the probabilities for n = 10 are practically equal to the probabilities in the distribution in the limit for n = ∞. This distribution in the limit is a Poisson distribution with mean value 1 and the probabilities of the distribution are given in Table 1 for comparison with the distributions deduced there.

In comparing the method employed by *Vogel* with the method proposed here it is found that while with *Vogel*'s method n! comparisons suffice, the number of comparisons in our method will be at least (2n—1) (2n—3) (2n—5) (4). 1. Correspondingly, it is found that in order to obtain significantly more correctly matched pairs as regards the 5 per cent. level with *Vogel*'s method, 4 or more correctly matched pairs must be obtained while with the method proposed here 3 or more pairs suffice. Significance as regards the 1 per cent. level is obtained in *Vogel*'s method with 5 or more correctly matched pairs and with the method proposed here with 4 or more correctly matched pairs.

Summary

A simple method of matching for evaluation of certain results obtained in investigation of a series of uniovular pairs of twins is mentioned. It applies to results of investigations which do not permit analysis by the usual statistical methods. It is proposed that matching should be performed from among all the results of the investigation placed in a random and unknown order. Equations are given for the probability of matching a certain number of twin pairs correctly in a random manner. The procedure which is appropriate when certain results of investigation obtained from limited materials of twins are concerned, is compared with the method in which the one series of partners is established in advance and the statistical advantage implied in the proposed method is mentioned.

Zusammenfassung

Es wird eine einfache Methode der Blindklassifikation für die Bewertung bestimmter Ergebnisse bei der Untersuchung einer Serie von eineiigen Zwillingspaaren angegeben. Man kann sie auf Untersuchungsergebnisse anwenden, die nicht mit den üblichen statistischen Methoden analysiert

werden können. Es wird vorgeschlagen, den Blindklassifikations-Versuch auszuführen, nachdem man alle Untersuchungsergebnisse zufällig und in einer unbekannten Anordnung gruppiert hat. Es werden Gleichungen für die Wahrscheinlichkeit angegeben, daß man eine bestimmte Anzahl von Zwillingspaaren zufällig richtig klassifiziert. Dieses Verfahren, das angewendet werden sollte, wenn bestimmte Untersuchungsergebnisse aus begrenztem Material ausgewertet werden sollen, wird verglichen mit der Methode, bei welcher die eine Serie von Paarlingen vorher festgelegt wird, und es wird der statistische Vorteil dargestellt, den die hier vorgeschlagene Methode bietet.

Résumé

L'auteur expose une méthode simple pour grouper certains résultats obtenus au cours des examens d'une série de jumeaux univitellins. Cette méthode s'applique à des résultats d'examens qui ne peuvent être analysés par des méthodes statistiques ordinaires.

L'auteur propose de grouper les résultats en se basant sur tous les résultats d'examens en les plaçant dans un ordre inconnu et selon les lois du hasard. Il donne des équations pour la probabilité de grouper correctement un certain nombre de jumeaux selon les lois du hasard. La méthode proposée est surtout indiquée lorsqu'il s'agit d'un matériel limité de jumeaux. En la comparant avec la méthode qui consiste à établir d'abord une série connue d'un des jumeaux, les avantages statistiques de la méthode suggérée sont démontrés.

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DAS TRENNVERFAHREN IN DER STATISTISCHEN BEWERTUNG VON ELEKTROPHEROGRAMMEN

Von

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Während wir bislang bei der statistischen Bearbeitung von Elektropherogrammen die Untersuchung auf eine signifikante Veränderung jeweils an den einzelnen Fraktionen vornahmen, erscheint es doch zuweilen vorteilhaft, von einem Elektrophoresediagramm in seiner Gesamtheit eine Aussage über seine Differenz gegenüber anderen gleicherweise erzielten Ergebnissen abgeben zu können. Diese Gedankengänge brachte *Herdan* erstmalig an dieser Stelle zum Ausdruck. Sie gaben ihm Veranlassung, seine Theorie der Entropie der Serumeiweißkörper und darauf aufbauend eine Methode der mathematisch-statistischen Bearbeitung von Elektrophoreseergebnissen zu entwickeln. Obgleich wir der *Herdan*schen Grundkonzeption der Entropie in der Anwendung auf die Serumproteinrelationen nicht in allen Punkten folgen können, so erscheint uns doch der Gesichtspunkt der Gesamtschau eines Elektrophoresespektrums für gewisse Fälle der Elektropherogrammbewertung sehr anregend.

In der Verfolgung ähnlicher Gedankengänge brachten wir ein Verfahren zur Anwendung, das wohl *Radhakrishna Rao* für den Zweck der Differentialdiagnose in der Medizin vorschlug, und das erstmals von *R. A. Fisher* als Trennverfahren (discriminatory analysis) publiziert worden war. Diese Methode der mathematisch-statistischen Beurteilung, die wir unter bestimmten Voraussetzungen in der Elektropherogrammbewertung als sehr zweckmäßig erachten, möchten wir im Rahmen dieser Ausführungen erläutern und zur Diskussion stellen.

Dieses von *Linder* für andere Untersuchungen in jüngster Zeit aufge-
griffene Verfahren gestattet die statistische Bewertung mehrerer veränder-
licher Faktoren zugleich, wobei jeder derselben eine eigene Bewertung er-
fährt. Dadurch tragen wir den unterschiedlichen Veränderungen der ein-
zelnen Fraktionen in ihren Relativwerten Rechnung.

Da wir es bei Elektrophoreseergebnissen gewöhnlich mit Prozentwerten
zu tun haben, die sich jeweils zu 100 ergänzen, so ist eine gewisse gegen-
seitige Bedingtheit der einzelnen Veränderungen selbstverständlich. Aus
diesem Grunde erscheint es doch nicht ganz ratsam, den Gedanken von
Herdan zu folgen und *alle* Fraktionen in der Trennformel zu erfassen. Eine
Auswahl der Fraktionen, welche die deutlichsten Veränderungen zeigen,
und bei denen sich dieselben gegenseitig nicht unmittelbar bedingen, ist
um so notwendiger, da die Signifikanzprüfung nach *Linder* in ihrer An-
wendbarkeit in Frage gestellt würde. Derselbe Autor weist darauf hin, daß
die Einbeziehung eines Maßes, das sehr eng mit einem zweiten korreliert
ist, bei der Rechnung zwar Mehrarbeit bedingt, aber den Wirkungsgrad
der Trennformel nicht erhöht. Wir bringen deswegen die Trennformel
dann nicht in Anwendung, wenn nur 2 Fraktionen innerhalb des Spektrums
deutliche Bewegungen erkennen lassen. In den Fällen, in denen mehr als
zwei Fraktionen stärkere Veränderungen aufweisen, lassen wir außer den
unveränderten eine der veränderten Fraktionen – meist die Albumine –
unberücksichtigt. Auf diese Weise findet das Gesamtbild der Veränderung
des Elektropherogramms am deutlichsten seinen realen Ausdruck, und die
Unabhängigkeit der Verschiebungen der Prozentwerte der Fraktionen
bleibt soweit als möglich gewahrt.

Stehen zur Unterscheidung von Einzeldingen aus zwei verschiedenen
Kollektiven von jedem der einzelnen Dinge die Meßwerte mehrerer ver-
schiedener quantitativer Merkmale (n an der Zahl) – in unserem Falle die
einzelnen Serumeiweißfraktionen – bereit, so ist es oft vorteilhaft, an Stelle
der einzelnen Werte zur Unterscheidung einen Index, der aus mehreren
derselben mittels einer geeigneten mathematischen Formel gebildet wird,
zu verwenden. Es gilt zunächst festzustellen, wie sich die beiden Mittel-
werte $\bar{x}_i$ der einzelnen Werte x_i des i-ten Merkmals (i = 1, 2, ..., n) in den
beiden Kollektiven voneinander unterscheiden. Nur diejenigen Merkmale,
deren Mittelwerte in dem einen Kollektiv erheblich von denen im anderen
Kollektiv abweichen, wird man dann für die Berechnung des Index ver-
wenden, weil die anderen zur Unterscheidung kaum einen Beitrag liefern
können und um den Rechenaufwand zu vermindern. Es ist vor allem daran
zu denken, einen Index, der linear aus den Werten $x_1, ..., x_m$ (m ist die
Anzahl der in die Rechnung eingehenden Merkmale, m $\leqslant$ n) zusammen-

gesetzt ist, zu berechnen. Die Formel für den Index würde dann lauten:

$$X = b_1 x_1 + \ldots + b_m x_m \tag{1}$$

Die x_i sind hier die Prozentsätze der einzelnen Eiweißfraktionen des elektrophoretischen Spektrums und die b_i sind gewisse zugehörige Faktoren.

Diese Faktoren $b_1, \ldots, b_m$ werden auf Grund der Meßwerte aus beiden Kollektiven (wenigstens dann, wenn der Stichprobenumfang aus beiden Kollektiven gleich groß ist) so berechnet, daß der Quotient aus der Differenz der Mittelwerte der Trennungsindizes aus den Kollektiven A und B

$$d_X = X_A - \overline{X}_B$$

und dem mittleren Fehler σ_d dieser Differenz möglichst groß wird. Aber selbst wenn der Stichprobenumfang aus beiden Kollektiven nicht gleich groß ist, dürften dieselben Bedingungen annähernd zutreffen. Genauere Angaben dazu gibt *Linder* (3). Sind aus beiden Kollektiven gleich viele Einzeldinge gemessen worden und ist m 2, d.h., gehen zwei Merkmale in die Rechnung ein, so dient zur Ermittlung von b_1 und b_2 das folgende System linearer Gleichungen:

$$\left. \begin{array}{l} b_1 S_{A, B} (x_1 - \overline{x}_1)^2 + b_2 S_{A, B} (x_1 - \overline{x}_1)(x_2 - \overline{x}_2) = d_1 \\ b_1 S_{A, B} (x_1 - \overline{x}_1)(x_2 - \overline{x}_2) + b_2 S_{A, B} (x_2 - \overline{x}_2)^2 = d_2 \end{array} \right\} \tag{2}$$

Die Bedeutung des Symbols $S_{A, B}$ wird bei Durchführung des Beispiels näher erläutert, wobei d_1 die Differenz der aus der ersten zu prüfenden Serumeiweißfraktion errechneten Mittelwerte am 1. (A) und 5. Versuchstag (B) darstellt; d_2 entspricht der Differenz der zweiten Fraktion.

$$d_1 = \overline{x}_{1A} - \overline{x}_{1B}$$
$$d_2 = \overline{x}_{2A} - \overline{x}_{2B}$$

Die weiteren Einzelheiten zur angeführten Formel (2) sind bei *Fisher* und *Radhakrishna Rao* nachzulesen.

An einem Beispiel unseres Untersuchungsgutes wollen wir das Trennverfahren erläutern. 35 Katzen wurden während eines bestimmten Zeitintervalls gewissen Versuchsbedingungen ausgesetzt und deren Einfluß auf das Serumeiweißspektrum in seiner Gesamtheit überprüft. Die Mittelwerte dieser 35 Tiere an den beiden Versuchstagen wiesen folgende Verhältnisse auf:

	Albumine	α_1-	α_2-	β_1-	β_2-	$\gamma-$	Globuline
A	52,9	4,4	12,1	5,3	8,2	17,1	
B	47,9	4,5	14,6	5,6	8,5	18,9	

Aus diesen Ergebnissen wird ersichtlich, daß sich die Veränderungen unter dem Einfluß der Versuchsbedingungen insbesondere an den Albuminen, den α_2- und γ-Globulinen auswirkten. Zum Zwecke der Signifikanzprüfung der Unterschiede der Seren beider Kollektive haben wir die α_2- und γ-Globuline in die Trennformel einbezogen, während wir die Albumine wegen ihrer großen negativen Korrelation zu den beiden anderen Fraktionen und der damit gegebenen mehr oder minder großen Abhängigkeit von jenen außer Betracht ließen.

Die Prozentsätze der α_2-Globuline, die wir mit x_1 bezeichnen wollen, wiesen vor der Behandlung der Katzen folgende Größen auf:

8,6	11,5	7,1	17,0	16,6	13,2	20,2	12,2	12,0	12,9
14,3	10,0	8,4	12,5	13,9	14,8	13,2	10,5	9,2	12,1
11,9	15,5	15,9	11,0	9,3	13,1	10,9	7,3	10,0	10,0
11,8	13,5	10,5	11,5	10,5					

Die Prozentsätze der γ-Globulinfraktion, die nunmehr mit x_2 bezeichnet werden, ergaben in gleicher Reihenfolge folgende Werte:

19,6	24,5	27,9	15,0	20,4	17,5	15,4	15,0	28,1	11,6
17,1	18,1	21,8	21,4	30,0	21,3	19,9	19,4	18,8	16,3
16,0	12,4	11,3	13,9	18,5	9,6	10,8	14,5	8,3	11,4
16,8	18,3	13,7	7,9	16,0					

Am 5. Versuchstag ergaben sich für x_1

13,8	11,0	8,4	20,0	18,6	15,3	15,4	12,5	13,1	12,7
18,2	13,5	12,4	15,3	15,9	15,4	15,5	11,9	11,9	13,7
14,5	17,7	16,9	14,3	12,6	18,6	18,4	15,1	15,0	11,2
12,2	15,9	15,5	12,3	15,2					

Für x_2 erhielten wir an diesem Tag folgende Werte:

18,2	26,2	31,9	14,2	17,8	16,5	20,1	32,4	27,5	16,4
21,0	17,4	22,7	22,6	30,5	21,9	20,6	25,2	20,2	17,9
18,9	14,4	14,4	13,2	18,3	10,3	12,7	14,7	9,2	12,5
17,7	19,3	11,9	14,7	19,0					

Wir betonen nochmals, daß in den vorstehenden Tabellen die 35 Katzenseren immer in der gleichen Reihenfolge erscheinen.

Zur Berechnung der Konstanten, die in Formel (2) auftreten, fertigten wir uns für beide Kollektive je eine Tabelle an. Das Schema der Tabelle für Kollektiv A geben wir in abgekürzter Form wieder:

Tabelle 1 (für Kollektiv A)

x_1	x_2	x_1^2	x_2^2	$x_1 x_2$
8,6	19,6	73,96	384,16	168,56
11,5	24,5	132,25	600,25	281,75
·	·	·	·	·
·	·	·	·	·
10,5	16,0	110,25	256,0	168,0
$S_A x_1$	$S_A x_2$	$S_A x_1^2$	$S_A x_2^2$	$S_A x_1 x_2$
= 422,9	= 598,5	= 5 381,91	= 11 209,01	= 7 180,46

Die Summen sowie auch später folgende Werte haben wir etwas aufgerundet.

Die Berechnung der in Formel (2) aufgeführten Faktoren gestaltete sich folgender-maßen:

1.
$$S_A (x_1 - \overline{x}_1)^2 = S_A x_1^2 - \frac{(S_A x_1)^2}{n} = 272$$

2.
$$S_A (x_2 - \overline{x}_2)^2 = S_A x_2^2 - \frac{(S_A x_2)^2}{n} = 975$$

3.
$$S_A (x_1 - \overline{x}_1)(x_2 - \overline{x}_2) = S_A x_1 x_2 - \frac{S_A x_1 \, S_A x_2}{n} = 51,13$$

Auf gleiche Weise ermittelten wir für das Kollektiv B folgende Werte:

1. $S_B (x_1 - \overline{x}_1)^2$ $=$ 222

2. $S_B (x_2 - \overline{x}_2)^2$ $=$ $1108,15$

3. $S_B (x_1 - \overline{x}_1)(x_2 - \overline{x}_2) = -241,78$

Aus diesen Werten ergibt sich für

$$S_{A, B} (x_1 - \overline{x}_1)^2 \qquad = \quad 272 + 222 \quad = \quad 494$$
$$S_{A, B} (x_2 - \overline{x}_2)^2 \qquad = \quad 975 + 1108 \quad = \quad 2083$$
$$S_{A, B} (x_1 - \overline{x}_1)(x_2 - \overline{x}_2) = - 51,13 - 241,78 \simeq - 293$$

Ferner ist

$$d_1 = \overline{x}_{1A} - \overline{x}_{1B} = -2,5$$
$$d_2 = \overline{x}_{2A} - \overline{x}_{2B} = -1,9$$

Nach Einsetzen aller so berechneten Konstanten in das Gleichungssystem (2) erhalten wir das folgende Gleichungspaar (2a):

$$494 b_1 - 293 b_2 = -2,5$$
$$- 293 b_1 - 2083 b_2 = -1,9$$

Es ergibt sich hieraus

$$b_1 = -0,006111$$
$$b_2 = -0,001772$$

Diese Werte werden so mit einem Faktor multipliziert, daß der kleinere Wert von beiden (in unserem Fall b_2) gleich 1,0 wird.

Die Trennformel lautet zu diesen Werten:

$$X = 3,449 \, x_1 + x_2$$

Um jedoch eine mathematisch gesicherte Aussage über auftretende Differenzen zwischen den Indizes treffen zu können, muß ein Signifikanzbeweis geführt werden, den wir von *Linder* übernehmen. Zu diesem Zweck hat *Mahalanobis* den Begriff des verallgemeinerten Abstandes (D) zwischen zwei Kollektiven eingeführt (hier zwischen A und B).

Die Rechnung gestaltet sich nun wie folgt:

$$\frac{1}{N_A + N_B - 2} \cdot 2D^2 = \overline{X}_A - \overline{X}_B$$

wobei $\overline{X}_A$ den Mittelwert der Indizes des A-Kollektivs darstellt.

Um für die Signifikanzprüfung die Berechnung der einzelnen Indizes zu ersparen, kann man genannte Formel umformen, denn es gilt

$$\overline{X}_A = b_1 \overline{x}_{1A} + b_2 \overline{x}_{2A} \quad \text{und}$$
$$\overline{X}_B = b_1 \overline{x}_{2B} + b_2 \overline{x}_{2B}$$

Für $2D^2$ ergibt sich

$$\frac{1}{N_A + N_B - 2} \cdot 2D^2 = b_1 \overline{x}_{1A} + b_2 \overline{x}_{2A} - b_1 \overline{x}_{1B} - b_2 \overline{x}_{2B}$$
$$= b_1 (\overline{x}_{1A} - \overline{x}_{1B}) + b_2 (\overline{x}_{2A} - \overline{x}_{2B})$$
$$= b_1 d_1 + b_2 d_2$$

Für unser Beispiel erhalten wir

$$2D^2 = 1{,}2675$$
$$D^2 = 0{,}6337$$

Zur Signifikanzprüfung benötigt man nun den sogenannten F-Wert:

$$F = \frac{N_A N_B (N_A + N_B - p - 1)}{(N_A + N_B)(N_A + N_B - 2)} \cdot D^2$$

Dabei ist p die Anzahl der in die Rechnung einbezogenen Merkmale und N_A bzw. N_B die Anzahl der Tiere in Kollektiv A bzw. B.

$$F \simeq 10{,}90$$

Diese Zahl ist an Hand der Tabelle für die F-Verteilung auf Signifikanz zu prüfen. (s. Tabelle E. WEBER, 3. Aufl. S. 434/35). Es ist dabei in den Tabellen die Zahl aufzusuchen, die bei $n_1 = p$ (bei uns = 2) und $n_2 = N_A + N_B - p - 1$ (= 67) steht. Wir sehen, daß der 0,5%-Sicherheitswert dort etwa $F = 5{,}80$ entspricht.

Da der von uns gefundene Wert für F weit höher liegt, ist der Unterschied zwischen den beiden Kollektiven statistisch signifikant.

Wir berechnen weiterhin die Größe der Korrelation zwischen den beiden Merkmalen x_1 und x_2, da eine weitgehende Unabhängigkeit der Verschiebung der geprüften Merkmale erstrebenswert ist. Eine direkte Abhängigkeit zweier Werte erscheint jedoch in der Praxis der Elektrophorese nur dann möglich, wenn die beiden Werte negativ miteinander korrelieren. Für den Korrelationskoeffizienten gilt nun folgende Formel:

$$r_{1\,2} = \frac{S_{AB}\,(x_1 - \overline{x}_1)\,(x_2 - \overline{x}_2)}{\sqrt{S_{AB}\,(x_1 - \overline{x}_1)^2 \cdot S_{AB}\,(x_2 - \overline{x}_2)^2}}$$

Da bei dieser Korrelationsprüfung beide Kollektive als Gesamtheit betrachtet werden, unterscheidet sich die Berechnung der einzelnen Faktoren von dem Weg, den wir oben (nach Formel 2) zur Anwendung brachten.

Im einzelnen werden folgende Größen bestimmt:

$$S_A\,x_1 + S_B\,x_1 \qquad = \qquad 932{,}8$$
$$S_A\,x_1^2 + S_B\,x_1^2 \qquad = 13\,032{,}44$$
$$S_A\,x_2 + S_B\,x_2 \qquad = \qquad 1\,261{,}9$$
$$S_A\,x_2^2 + S_B\,x_2^2 \qquad = 24\,891{,}43$$
$$S_A\,x_1\,x_2 + S_B\,x_1\,x_2 = 16\,603{,}47$$

Es ergibt sich für

$$r_{1\,2} = \frac{-\,212{,}2}{\sqrt{602 \cdot 2147}}$$
$$= -0{,}187$$

Zur Beurteilung des Korrelationskoeffizienten wird dieser nach der Formel

$$z = \frac{1}{2}\ln\frac{1 + r}{1 - r}$$

in z umgerechnet (s. auch E. Weber, 3. Aufl. S. 446).

Der unserem Korrelationskoeffizienten entsprechende Wert für z beträgt

$$z = 0{,}19$$

Der mittlere Fehler hierzu ist

$$m_z = \frac{1}{\sqrt{N_A + N_B - 3}}$$
$$= 0{,}123$$

Da z kleiner ist als $3m_z$, besteht keine signifikante Korrelation zwischen x_1 und x_2.

Bei der Darstellung verschiedener Methoden zur statistischen Bewertung von Elektropherogrammen hatten wir u. a. den sog. U-Test in Anwendung gebracht (7).

Diese statistische Methode kann auch auf die Trennindizes der 70 Seren unserer 2 Kollektive angewandt werden. Dabei gestaltete sich unser Vorgehen derart, daß nach Berechnung der einzelnen Indices dieselben in natürlicher Reihenfolge geordnet und mit den entsprechenden Rangzahlen – wie in Tabelle 2 ersichtlich ist – versehen wurden.

Tabelle 2

Trennindizes in natürlicher Reihenfolge (Kollektive A und B)

39,7	43,8	45,9	47,6	48,4	49,3	49,9	50,5	50,6	50,8
1	2	3	4	5	6	7	8	9	10
51,1	51,8	52,4	52,6	53,2	54,8	55,6	56,1	**56,1**	57,0
11	12	13	14	15	16	17	18,5	18,5	20
57,1	57,1	57,5	58,0	**59,8**	**60,2**	**60,9**	**60,9**	**61,2**	**61,8**
21,5	21,5	23	24	25	26	27,5	27,5	29	30
62,5	63,0	**64,0**	64,2	64,5	64,9	**65,2**	65,4	**65,4**	**65,5**
31	32	33	34	35	36	37	38,5	38,5	40
65,8	65,9	66,1	**66,2**	66,4	**66,8**	**68,9**	**69,3**	69,5	**71,4**
41	42	43	44	45	46	47	48	49	50
72,3	**72,7**	**72,7**	**73,2**	73,6	**74,1**	**74,1**	**74,5**	**75,0**	**75,4**
51	52,5	52,5	54	55	56,5	56,5	58	59	60,5
75,4	**75,5**	**76,2**	77,7	77,9	**82,0**	**83,2**	**83,8**	85,1	85,3
60,5	62	63	64	65	66	67	68	69	70

Die Trennindizes des Kollektivs B haben wir in der Tabelle durch fette Schrift gekennzeichnet. Die Summe der Rangzahlen der in fetter Schrift gedruckten Werte beträgt 904,5. Daraus folgt:

$$U = 950,5$$
$$E(U) = 612,5$$
$$\sigma_u = 85,1$$

Es ergibt sich weiterhin:

$$t = \frac{337,0}{85,1}$$
$$t = 3,97$$

Bei Prüfung der Differenz zwischen den Werten der α_2-Globuline am 1. und 5. Versuchstag erhielten wir, wie an anderer Stelle von uns mitgeteilt wird, einen t-Wert von

3,68 (7). Durch Anwendung der Indizes läßt sich die Signifikanz deutlicher herausstellen als bei Anwendung einer Fraktion allein. Diese Methode dürfte somit für Grenzfälle in der Bewertung von Elektropherogrammen von Wichtigkeit sein.

Die Besprechung der Frage, wie ein Serum, von dem nur bekannt ist, daß es bestimmt einer von zwei untersuchten Gruppen angehört, ohne daß man wüßte, welcher von beiden es zuzuordnen ist, klassifiziert werden kann, beginnen wir mit der Darlegung der Formel zur Berechnung des «verallgemeinerten Abstands» nach *Mahalanobis*. In den Beispielen, die bei 3 und 6 zur Methode von *Mahalanobis* angegeben worden sind, werden jeweils 3 Gruppen (A, B und C) von Werten untereinander verglichen. Es wird dann die Frage erörtert, ob beispielsweise die Gruppe C der Gruppe A oder der Gruppe B näher steht (einen geringeren Abstand von Gruppe A hat als von Gruppe B). Zur Entscheidung dieser Frage wird einmal die Trennformel

$$X_{AC} = b_1 (A, C) x_1 + b_2 (A, C) x_2 \qquad (3)$$

und zum anderen die Trennformel

$$X_{BC} = b_1 (B, C) x_1 + b_2 (B, C) x_2 \qquad (4)$$

berechnet, wie wir die Berechnung solcher Trennformeln angegeben haben. Die Indizes A und C bzw. B und C besagen hier, daß zur Berechnung der Formel (3) die Werte aus den Gruppen A und C in die Rechnung eingehen, während zur Berechnung der Formel (4) die Werte aus den Gruppen B und C herangezogen werden. Anschließend wird ebenso, wie wir das bereits gezeigt haben, der verallgemeinerte Abstand einmal zwischen den Gruppen A und C und zum anderen zwischen den Gruppen B und C berechnet. Man faßt die Gruppen, deren verallgemeinerter Abstand bei der Rechnung als am größten befunden wird, als stärker voneinander unterschieden auf, als die anderen. Formal läßt sich diese Rechnung auch durchführen, wenn die Gruppe C aus einem einzigen Element (Serumeiweißspektrum) besteht. Das Besondere dabei ist lediglich, daß dann in Gruppe C die Werte

$$S_C (x_1 - \overline{x}_1)^2, \ S_C (x_2 - \overline{x}_2)^2 \ \text{und} \ S_C (x_1 - \overline{x}_1) (x_2 - \overline{x}_2)$$

alle gleich Null sind, da sowohl x_1 als auch x_2 gleich ihre eigenen Mittelwerte sind. Dabei ist der Ausdruck «Mittelwert» naturgemäß in einem etwas veränderten Sinn gebraucht, da man eigentlich von einem Mittelwert aus einer einzigen Zahl nicht sprechen kann. Trotzdem lassen sich die verallgemeinerten Abstände berechnen und, sofern über die Häufigkeit des

Auftretens der Gruppen A und B unter den zur Untersuchung gelangenden Seren nichts bekannt ist oder, sofern man weiß, daß beide gleich häufig auftreten, mag es zur Klassifizierung des Individuums C genügen, festzustellen, zu welcher der beiden Gruppen A und B sein verallgemeinerter Abstand kleiner ist.

Wir nehmen an, ein Katzenserum C habe folgende Relativwerte:

Albumine	41,9%
α_1-Globuline	6,0%
α_2-Globuline	18,2%
β_1-Globuline	3,9%
β_2-Globuline	9,1%
γ-Globuline	21,0%

Dann sind die Größen, die für x_1 (α_2-Globuline) und x_2 (γ-Globuline) zur Berechnung verwendet werden, 18,2 (x_1) bzw. 21,0 (x_2). Gegenüber dem entsprechenden Mittelwert der Gruppe A ist dann $d_1 = -6,1$ und $d_2 = -3,9$. Wir erhalten dann mit den früher angegebenen Summenwerten aus Gruppe A, da der Einzelwert C nichts dazu beisteuert, die Bestimmungsgleichungen für $b_1(A, C)$ und $b_2 (A, C)$:

$$d_1 = \overline{x}_{1A} - x_1C$$
$$d_2 = \overline{x}_{2A} - x_2C$$
$$b_1 \cdot 272 - b_2 \cdot 51 = -6,1$$
$$- b_1 \cdot 51 + b_2 \cdot 975 = -3,9$$

aus denen sich $b_1 = -0,0234$ und $b_2 = -0,0522$ ergibt.

Nach den ebenfalls weiter oben angegebenen Formeln folgt weiter:

$$2D^2{}_{AC} = 34 \left[(-6,1) \cdot (-0,0234) + (-3,9) \cdot (-0,0522)\right]$$
$$= 11,8$$

Analog ergibt sich mit Gruppe B:

$$b_2(B, C) \cdot 222 - b_3(B, C)\ 242 = -3,6$$
$$- b_2(B, C) \cdot 242 + b_3(B, C)\ 1108 = -2,0$$

und daraus

$$b_1 = -0,02387 \text{ und } b_2 = 0,00702$$

sowie

$$2 D^2{}_{BC} = 3,4.$$

Der Abstand zur Gruppe B ist also kleiner als der zur Gruppe A, d. h., dieses Serum ist wahrscheinlich dem Kollektiv B zuzuordnen.

Somit erscheint dieses von uns angeführte Trennverfahren für die Bewertung sowohl von Elektropherogramm-Mittelwerten als auch für die Zuordnung von Einzelergebnissen tauglich.

Zusammenfassung

Es wird das von *Fisher* angegebene Trennverfahren in der Anwendung auf die statistische Bewertung von Elektropherogrammen theoretisch und praktisch ausgeführt.

Summary

The application of the discriminatory analysis *(R. A. Fisher)* for the statistical evaluation of electrophoresis data is demonstrated theoretically and practically.

Résumé

L'application de la «discriminatory analysis» *(R. A. Fisher)* pour l'évaluation statistique des électrophérogrammes est demontrée en théorie et avec des exemples.

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ON THE INHERITANCE OF THE
Gm SERUM GROUP

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and M. HAUGE

In 1956 *Grubb* devised a method which permitted grouping of human sera by a red cell agglutination technique (3).

The principle of the method is that Rh-positive human red cells of group 0, after coating with certain "incomplete" Rh antibodies, will be agglutinated by certain sera, mainly from patients with rheumatoid arthritis (3, 4, 5, 6). *Grubb* and *Laurell* found that about 60% of normal human sera were able to *inhibit* this agglutination. From further investigations it appeared probable that the inhibitor was located in the gamma-globulin fraction of the serum. Hence the names Gm(a+) for the phenotype of the inhibitory sera and Gm(a–) for that of the non-inhibitory sera.

The difference between Gm(a+) and Gm(a–) individuals was not considered to be so absolute as that between the blood groups A and B, but rather to be analogous to the A_1-A_2 distinction. The difference between the inhibitory capacity of Gm(a+) and Gm(a–) sera was at least tenfold and usually permitted ready distinction. An "intermediate" type may, however, be encountered, but is very rare (3, 4, 6).

By using a simple slide technique, *Moullec, Kherumian, Sutton* and *Espagnon* (11) were able to confirm the reliability of the Gm grouping.

An investigation of the Gm groups in 28 families, carried out by *Grubb* and *Laurell* (6), supported the assumption that the existence of this inhibitor in human serum was hereditary, possibly determined by an autosomal gene, capable of expressing itself in the heterozygous condition.

This gene was denoted by the symbol Gm[a]. The symbol Gm without any superscript was adopted for the presumed allele(s) at the same locus. The Gm serum group was not found to be closely correlated with sex, the AB0 nor the Rh blood group systems. In about 30 cases no correlation was found between the Gm group and the MNS, P, Kell, Lewis and Lutheran systems. Finally, in 46 persons the Hp and the Gm serum groups were determined as well as the secretor characters with regard to ABH and Le[a]. The results obtained rendered no evidence against the assumption that the Hp, Gm and Le groups were independent of one another (7).

In a series of 300 donors, *Moullec et al.* (11) found 54.3% Gm(a+) individuals and 45.7% Gm(a–). Another series comprising 16 families confirmed the family findings of *Grubb* and *Laurell*. In one family *Moullec* and co-workers observed that the father and a son were both Gm(a+), but in both the inhibitory factor was weaker than normal; they expressed the view that this variant may also be hereditary.

At birth, special conditions are present (1, 9, 11). The child is invariably born with the Gm group of its mother, indicating that the Gm-group-determining gamma-globulin has passed from mother to child. This has been confirmed without any exceptions in studies of cord blood from 165 infants (10). Of these, 113 were studied repeatedly during their first months. At the age of 4 months, almost all the infants were Gm(a–), and only after that time did the child begin to develop its own Gm group; at the age of 8 months, the Gm group of the infant does not yet seem to be fully developed.

As the existing material for testing the genetic theory advanced by *Grubb* and *Laurell* still is limited an extensive investigation of the Gm groups was considered desirable. Furthermore, the aim of the present study is to provide figures for the calculation of gene frequencies in Denmark and to elucidate the relationship between the Gm serum group and the erythrocyte antigens as well as the haptoglobins. Finally, an analysis will be undertaken to see whether any genetic linkage can be detected between the Gm group and the blood and haptoglobin group loci and sex.

Methods

All the determinations of the Gm serum groups were carried out by the same investigator (L.-J.). A slightly modified form of the technique described by *Grubb* (6) has been used throughout.

Determination of the Gm serum groups.

Diluent. Grubb used phosphate-buffered saline, pH 7.2, as the diluent for the test sera, for the suspension of red cells and for washing. The agglutination of anti-D-coated

red cells by rheumatoid arthritic sera certainly does depend upon the ionic strength and pH of the suspension (4), but it was found that unbuffered saline is just as good a diluent as buffered saline.

Red cells. *Grubb* and *Laurell* (6) and *Moullec et al.* (11) preferred human red cells which were supposed to be D-homozygous. So far, we have been unable to find any difference between D-heterozygous and D-homozygous cells when these are used in the agglutination test after coating with "incomplete" anti-Rh. In the investigations reported here, red cells of the Rh genotype cDE/cde and always from the same donor were employed. The red cells were stored in acid-citrate-dextrose solution (Pharmacopeae Danicae) at 4°C. for a maximum of 3 days.

Sera containing "incomplete" anti-Rh. Anti-D sera of a titre of at most 1:4 in saline and at least 1:256 against trypsinized Rh-positive red cells were used. Anti-DE or anti-CD sera may also be used. Even high-titred sera may be useless for coating the cells. The coating capacity is apparently correlated to a great extent with the Gm group of the anti-D serum. Most of the useful sera were from Gm(a+) donors (4). Of 66 high-titred anti-D sera which we investigated, only six proved to be useful for coating, and five of these were Gm(a+). In the investigations reported here, anti-D serum from the same donor was used throughout. Judged by the indirect Coombs technique, this serum had a titre of 1024. It was diluted 1:10 with saline before coating.

Coating of red cells with anti-D. An amount of 1 ml of packed cells which had been washed 3 times in saline was incubated with 9 ml of serum dilution at 37°C. for 2 hours. The tubes were shaken now and then during incubation. The cells were then washed 4 times in saline, and it was checked if the coated cells were rapidly and strongly agglutinated by rabbit anti-human-globulin serum. A 0.5% suspension of coated red cells in saline was prepared immediately before use.

Rheumatoid arthritic sera were selected from specimens collected from patients with active rheumatoid arthritis. The sera were not inactivated and were stored at —20°C.

Agglutination test. This was performed in test tubes with round bottoms, measuring 70 × 10–11 mm. The volumes used were 0.25 ml of serum dilution and 0.25 ml of the 0.5% suspension of coated Rh-positive red cells. All serum dilutions from 1:5 to 1:1280 were tested by the standard twofold dilution titration technique. The test tubes were allowed to stand at room temperature for 3 hours. Using a concave mirror, the results were read both by inspecting the pattern of the settled cells and after gentle shaking. The following controls were included: (1) a saline suspension of the coated Rh-positive red cells; (2) a tube with serum dilution 1:5 and uncoated Rh-positive red cells. When testing rheumatoid arthritic sera for their capacity to agglutinate coated human red cells, cell samples coated with several different anti-Rh sera should be used. In our hands, 80 out of 450 sera from patients with rheumatoid arthritis gave agglutination of the anti-D coated red cells, but the strength and avidity of the reactions were fairly variable. A primary selection of agglutinating rheumatoid arthritic sera may be done by choosing sera with a high titre in the Waaler-Rose test (agglutination of sheep red cells coated with non-agglutinating doses of rabbit anti-sheep hemolysin), but even sera with a high titre in this test may be negative when examined for their capacity to agglutinate anti-D-coated human red cells.

Selection of rheumatoid arthritic sera for the agglutination-inhibition test. The sera to be used in the agglutination-inhibition test must be high-titred in the agglutination test, but must not show prozone. Moreover, the agglutination must be inhibited by pooled human gamma-globulin (6).

In our experience, about 10% of rheumatoid arthritic sera with a positive agglutination reaction can be used in the agglutination-inhibition test. Most of such rheumatoid arthritis sera are Gm(a−) (8).

Agglutination-inhibition test (Gm grouping). The general technique is the same as in the agglutination test. An amount of 0.12 ml of the serum to be assayed for its content of inhibitor is mixed with 0.12 ml of the selected rheumatoid arthritic serum, diluted with saline to contain 20 agglutinating doses. After standing at room temperature for 15 minutes, 0.25 ml of the 0.5% suspension of coated red cells was added; the test tubes were agitated and then allowed to stand at room temperature for 3 hours. The results were read as described above.

The sera to be investigated were tested in the following dilutions: 1:4, 1:8, 1:16 and 1:32. The following controls were included: (1) 0.12 ml of the serum to be tested diluted 1:4 plus 0.12 ml saline; (2) 0.12 ml of rheumatoid arthritic serum of the dilution used in the test plus 0.12 ml saline; (3) 0.25 ml saline. Amounts of 0.25 ml of the 0.5% suspension of coated red cells were added to all control tubes.

All sera tested for their content of inhibitor were assayed against two rheumatoid arthritic sera, and control sera from the same two Gm(a+) and Gm(a−) individuals were always included.

Some variation in the inhibitory capacity may be observed in repeated studies on the same serum, largely depending on the test sera used and the degree of coating of the red cells.

It is of primary importance that the two systems – each representing its own rheumatoid arthritic serum – are adjusted so that the daily Gm(a+) control serum shows complete inhibition at least in the dilutions 1:4 and 1:8. If this is not the case, either the anti-Rh serum or the rheumatoid arthritic sera must be further diluted. In the present investigations, sera from the same two patients with rheumatoid arthritis were used throughout. Both had an agglutination titre of 1280–2500 against anti-D-coated human red cells and were diluted 1:25 or 1:50 in saline before use in the agglutination-inhibition test.

All sera must be stored carefully and, after thawing-out, must be shaken thoroughly, so that each individual small serum sample is representative of the serum to be investigated.

Determination of the Haptoglobin groups.

All determinations of the Haptoglobin groups in the present material were carried out by one of the authors (G.-J.) by means of the starch gel technique described in detail earlier (2).

All tests were carried out as blind tests.

Material

The material in the present investigation is composed of three groups of individuals: (1) unrelated persons, (2) families consisting of the two parents and at least one child, and (3) monozygous and dizygous twins.

The group of *unrelated persons* includes a large number of individuals from all over the country, collected at random; the parents in a material consisting of newborn infants and their fathers and mothers, investigated

by one of us (10), and a number of single twin partners in pairs where the co-twin has not yet been examined.

In the calculations of gene frequencies all parents of the present family material as well as one twin out of each of the complete twin pairs (in the dizygous pairs one was picked out at random) have been included also. The total number of unrelated persons appears from Table 1.

Table 1

Distribution of the Gm serum groups in 1084 unrelated individuals

| | Gm(a+) | | Gm(a—) | |
	observed	expected	observed	expected
Males	307	310.4	251	247.6
Females	296	292.6	230	233.4
Total (both sexes)	603 = 55.63%		481 = 44.37%	

$$\chi^2 = 0.173 \quad 0.70 > P > 0.50 \quad (d.f. = 1)$$

The *family material* comprises 181 complete families with 438 children tested (all being more than 5 years of age). All families were unselected as far as blood and serum groups are concerned.

The families are listed in the appendix; those with a G before the family number were collected mainly by one of the authors (G.-J.). The blood grouping in these cases was done in the Institute of Forensic Medicine; they are all unselected "normal" families. 21 of these, however, have previously been collected, examined and published by *Grubb* (3) (families nos. G11 – G31). These Swedish families have not been included in the calculation of gene frequencies. The families with H attached to the family number (in the appendix) were investigated as far as the blood groups are concerned by another of the authors (M.H.). The majority of these families had blood samples taken in connection with an investigation of an abnormality of the spine. When analysing these families separately, it was found that they differed in no respect (i.e. genefrequencies, distribution of mating types and of the children within the families) from expectation, based on Mendel's laws and on the gene frequencies found in the remaining material, and they may consequently be considered as collected in a way unrelated to the character under consideration.

The majority of the *twin material* forms part of an unselected "twin population" which is at present being collected at the Institute of Human Genetics, comprising all twins born in Denmark within a definite period. There was some selection for monozygous pairs in the material given here, because in a number of cases the polysymptomatic similarity test disclosed such striking and important discrepancies between partners as regards eye colour, hair colour and/or stature (in pairs of same sex) that

no blood samples were taken. Similarly, only a very small number of twin pairs of different sex have been included here. The blood grouping and the polysymptomatic similarity tests have in the main been carried out at the Institute of Human Genetics. The total number of twin pairs tested appears from Table 12.

The analysis of the family material has been carried out on the assumption of unifactorial inheritance, i.e. that the Gm serum group is determined by the genes of one locus, with one gene, Gm^a, being able to manifest itself in the heterozygous state, so that individuals of the phenotype Gm(a+) possess one or two Gm^a genes, and those with the phenotype Gm(a−) lack the Gm^a gene, the corresponding genotype being denoted GmGm.

In testing the family material, a method has been adopted which was worked out in detail and described by *C. A. B. Smith* (12); it is in principle mainly based on previous proposals by *Hogben*, *Haldane* and *Fisher* (for references, see *Smith*). In this method due respect is paid to the fact that children from say the phenotype mating Gm(a+) × Gm(a−) are not independent samples from a homogenous population. The tests are carried through for each of the parent (phenotype) combinations separately; two comparisons are made within each, considering first matings where the presence of at least one Gm(a−) child discloses the genotype of the parents. Here the total yield of Gm(a−) children is compared with the number expected from the Mendel formulae. Secondly, it is tested whether there is a satisfactory division between matings with and without recessive children, taking the gene frequencies in account.

Results

Table 1 gives the results of the Gm grouping in unrelated individuals, tabulated according to sex. The difference between males and females is clearly insignificant. The pooled number of males and females is therefore used in the calculation of the frequencies. Assuming the phenotype Gm(a−) to represent the genotype GmGm the gene frequencies are estimated in the conventional way:

the frequency of the gene Gm $= \sqrt{0.4437} = 0.666$

and the frequency of the gene Gm^a $= 1 - \sqrt{0.4437} = 0.334$.

The genotype frequencies are therefore:

Gm^{a}Gm^a: 0.1115   Gm^{a}Gm: 0.4448   GmGm: 0.4437.

These frequencies have been used in the analysis of the family material.

As appears from Table 2 the Gm group seems to be independent of the blood groups indicated and the Hp group. By the chi-square method all P-values were found to be greater than 0.05 and equally distributed on both sides of P=0.50.

Table 2

Gm-groups in relation to blood groups and Hp groups

	0	A_1	A_2	B	A_1B	A_2B	M	N	MN	S	s
Gm(a+)	128	101	22	31	6	·9	105	71	131	169	134
Gm(a—)	96	75	21	27	4	8	75	54	120	168	119

	R_1r	R_2r	rr	R_1R_1	R_1R_2	R_0r	R'r	R''r	R_1R_z	R_2R_z
Gm(a+)	112	40	50	63	28	2	2	2	0	6
Gm(a—)	80	31	48	38	33	2	1	1	1	3

	P+	P—	Le(a+)	Le(a—)	K+	K—	Lu(a+)	Lu(a—)
Gm(a+)	230	75	55	247	13	293	13	128
Gm(a—)	162	73	46	188	10	225	7	97

	Fy(a+)	Fy(a—)	Hp 1—1	Hp 2—2	Hp 2—1
Gm(a+)	186	111	43	119	158
Gm(a—)	150	86	43	92	117

Table 3

Observed and expected distribution of mating types

Mating type	No. obs.	No. exp.	χ^2
Gm(a+) × Gm(a+)	55	56.0	0.02
Gm(a+) × Gm(a—)	92	89.4	0.08
Gm(a—) × Gm(a—)	34	35.6	0.07
Total no. of matings	181	Total χ^2	0.17 (d.f. = 2)
			0.95>P>0.90

Tables 3–11 give the results of the analysis of the family material. In Table 3 the observed and expected incidence of the various mating types are shown. The agreement is satisfactory. In Table 4 the distribution of families of mating type Gm(a+) × Gm(a+) is indicated. The families with at least one recessive child disclosing the genotype of the parents are treated separately and according to size in Table 5, where the number of recessive children expected on the hypothesis mentioned above is set out. The difference between this and the number observed is insignificant. In Table 6, the division between families with and without recessive children is tested,

Table 4

Observed distribution of families of mating type Gm(a+) × Gm(a+)

No. of children in family of group Gm(a—)	No. of children in family tested for Gm group						Total
	1	2	3	4	8	9	
0	7	22	6	3	1	1	40
1		2	3	4	1		10
2			2	1	1		4
3				1			1
Total no. of families	9	27	11	6	1	1	55
Total no. of families with at least one Gm(a—) child	2	5	5	3	0	0	15

(Figures in cells indicate no. of families)

Table 5

Mating type Gm(a+) × Gm(a+)
Analysis of families with at least one Gm(a—) child

No of children in family	No. of families	No. of Gm(a—) children		
		obs.	exp.	variance
1	2	2	2.000	0
2	5	7	5.715	0.610
3	5	6	6.485	1.315
4	3	6	4.389	1.260
Total	15	21	18.589	3.185

$$\chi^2 = (\text{Obs. - Exp.})^2 \div \text{var.} = 1.825 \ (\text{d.f.} = 1)$$
$$0.20 > P > 0.10$$

Table 6

Mating type Gm(a+) × Gm(a+)
Analysis of families with and without children of group Gm(a—)

No. of children in family	Total no. of families	No. of families with at least one Gm(a—) child		
		obs.	exp.	variance
1	9	2	1.438	1.208
2	27	5	7.560	5.443
3	11	5	4.065	2.563
4	6	3	2.623	1.476
8	1	0	0.575	0.244
9	1	0	0.591	0.241
Total	55	15	16.852	11.175

$$\chi^2 = 0.307 \ (\text{d.f.} = 1) \ 0.70 > P > 0.50$$

Table 7

Observed distribution of families of mating type Gm(a+) × Gm(a—)

No. of children in family of group Gm(a—)	No. of children in family tested for Gm group					Total
	1	2	3	4	5	
0	9	27	2	1	1	40
1	5	11	8	1		25
2		11	11	1	1	24
3			1	2		3
Total no. of families	14	49	22	5	2	92
Total no. of families with at least one Gm(a—) child	5	22	20	4	1	52

Figures in cells indicate number of families

Table 8

Mating type Gm(a+) × Gm(a—)
Analysis of families with at least one Gm(a—) child

No. of children in family	No. of families	No. of Gm(a—) children		
		obs.	exp.	variance
1	5	5	5.000	0
2	22	33	29.326	4.884
3	20	33	34.280	9.800
4	4	9	8.532	3.128
5	1	2	2.581	1.082
Total	52	82	79.719	18.894

$\chi^2 = 0.275$ (d.f. = 1) $0.70 > P > 0.50$

Table 9

Mating type Gm(a+) × Gm(a—)
Analysis of families with and without children of group Gm(a—)

No. of children in family	No. of families	No. of families with at least one Gm(a—) child		
		obs.	exp.	variance
1	14	5	5.597	3.361
2	49	22	29.385	11.763
3	22	20	15.393	4.623
4	5	4	3.750	0.938
5	2	1	1.550	0.349
Total	92	52	55.675	21.034

$\chi^2 = 0.642$ (d.f. = 1) $0.50 > P > 0.30$

Table 10

Distribution of families of mating type Gm(a—) × Gm(a—)

No. of children in family tested	Observed no. of families	Total no. of children of group Gm(a+)	Gm(a—)
1	7	—	7
2	13	—	26
3	5	—	15
4	5	—	20
5	1	—	5
6	1	—	6
7	2	—	14
Total	34	0	93

Table 11

Summary of tests on the family material

Test	Mating	χ^2	d. f.
No. of Gm(a—) children, given f	Gm(a+) × Gm(a—)	0.275	1
No. of Gm(a—) children, given F	Gm(a+) × Gm(a+)	1.825	1
Sum of f, given n	Gm(a+) × Gm(a—)	0.642	1
Sum of F, given N	Gm(a+) × Gm(a+)	0.307	1
Total		3.049	4

$$0.70 > P > 0.50$$

Symbols: n = total number of families of mating type Gm(a+) × Gm(a—).
f = no. of families of mating type Gm(a+) × Gm(a—) with at least one Gm(a—) child.
N = total number of families of mating type Gm(a+) × Gm(a+).
F = no. of families of mating type Gm(a+) × Gm(a+) with at least one Gm(a—) child.

Table 12

The Gm groups in a twin series (119 pairs)

	Gm groups identical	Gm groups different	Total
Presumably monozygous twins (†)	obs. 68 pairs exp. 68 pairs	obs. 0 pairs exp. 0 pairs	68 pairs
Dizygous twins	obs. 33 pairs exp. 37.1 pairs (††)	obs. 18 pairs exp. 13.9 pairs(††)	51 pairs

† i.e. of identical sex, blood groups, Hp groups and of high concordance in the similarity test.
†† The calculation of the expected numbers is based on the gene frequencies.

the expectations being based on the gene frequencies. The agreement is again satisfactory. Table 7 shows the distribution of families of the second mating type, Gm(a+) × Gm(a–); these families are then tested as described for the first mating type. Tables 8 and 9 give the comparisons between the observed and expected numbers; no significant deviations are found. In Table 10 the families of the third mating type Gm(a–) × Gm(a–) are tabulated according to size; as expected all children were found to be Gm(a–). The results of all tests are summarized in Table 11.

The findings in the twin material, which appear from Table 12, also support the hypothesis of a hereditary nature of the Gm group as all presumably monozygous twins (of identical sex, blood groups, Hp group and of high concordance in the similarity test) exhibit identical Gm groups. For the sake of completeness it can be stated that ten of the monozygous pairs had been reared apart from their earliest childhood. The distribution in the dizygous pairs is in fair agreement with expectation, based on the gene frequencies.

A full report of the linkage relations of the Gm group locus will be given later.

As this investigation is intended to cover normal conditions only, nothing can be said about possible relationships between the Gm group and diseases.

Discussion

The existence of a newly identified, hereditary, normal character in human blood (serum) has been confirmed by the present investigation, which gives very strong support to the theory advanced previously that the presence of this factor, a special inhibitor, is determined by a single, autosomal gene denoted Gm^a, which is able to express itself in single (and double) dose, identified as the phenotype Gm(a+). Some reservation has, however, to be made in the case of small children, as it has been found that the newborn infant carries the Gm phenotype of its mother, and it cannot yet be established at what age the child develops its own, inherited Gm group fully.

During the present investigation it was found that some variation in strength of the inhibitory action exists, which is in any case partly explained by small changes in the agglutination-inhibition system, which may occur even from day to day. In addition to the technical prescripts mentioned earlier it has to be considered that the time which elapses between the collecting of serum samples and the testing may influence the sera differ-

ently. Some evidence in this direction emerges from the fact that a variation in strength was observed between monozygous twin partners (in two cases), but only when the samples had been stored for more than 20 months (at –20° C.). A variation may of course also be influenced by genetic factors in other cases; this aspect has not been studied in the present investigation because all tests were carried out as blind tests without the possibility of comparing the reactions of related individuals directly. This demands special studies where the sera to be compared must be taken at the same time and tested on the same day, using the same agglutination-inhibition systems. Weak inhibitors possibly exist and may be hereditary, and finally the problem of a dosage effect has to be elucidated.

At the moment, nothing definite can be said about the nature or number of the other allele(s) at the Gm locus, nor is it justified to denote the Gm^a gene as a real dominant as the other allele(s) at this locus may turn out later to be identifiable by means of a different technique. Furthermore, several systems of the same nature may exist with only minor differences. The identity of the reactions in the agglutination-inhibition systems used in the present study and in the systems used by *Grubb* has been confirmed in several cases.

It can be stated that by carrying out the tests as indicated here we are able to define a new normal character in man which is most probably determined by a single gene.

This means a valuable new tool in dealing with problems of genetic identity and relationship. Thus it is possible to increase the reliability of the diagnosis of monozygosity in twins. Furthermore, this new system may, with certain precautions, be of value in cases of disputed paternity.

From a forensic point of view the Gm group seems to present two definite advantages when compared with other recently found blood group systems: (1) the distribution of gene frequencies is rather favourable, giving a theoretical exclusion rate of 0.0677; (2) test sera seem to be reasonably easily accessible. However, before the Gm system may be used forensically, a few problems must be elucidated more fully. The technique is rather complex and time-consuming, and other sera with similar, but not identical qualities may appear. The Gm grouping cannot be considered reliable within the first year of life, because, as mentioned above, during the first months after birth the child invariably carries the Gm phenotype of its mother, and, in any case at an age of 8 months, the children of genotype Gm^{a}Gm^a and Gm^{a}Gm do not seem to have developed their inherited Gm group fully. An essential question is therefore: at what age have the children, carrying a Gm^a gene, developed their Gm phenotype fully? These

two factors reduce the applicability of the Gm group in cases of disputed paternity within the first year of the child's life. It must, however, be emphasized that use of the Gm system before the child's own, genetically determined Gm group is fully established does not involve the risk of false exclusions as the combination: mother Gm(a–) and child Gm(a+) is the only basis for an exclusion. Neither the transfer of the maternal inhibitory factor transplacentally to the child nor an undeveloped Gm^a property in the child will give rise to this combination, but in the latter case a possibility of exclusion may admittedly be lost. Finally, it ought to be stressed that only indirect evidence exists concerning the constancy of the Gm groups through the rest of life.

Provided impeccable technique and clearcut positive and negative results are obtained, a forensic use of the Gm system in cases of disputed paternity might be considered. An exclusion based upon the Gm system can at present be regarded as an evidence against paternity only when connected with other factors, pointing in the same direction.

The Gm serum group may also enter the deplorably short row of genetic markers for use in linkage studies, being as they are reasonably easy to determine and presenting a satisfactory distribution of phenotypes in the population.

At present, it is not possible to evaluate the importance of the Gm group in genetical-anthropological research. To the knowledge of the authors only two small materials have hitherto been published, both from Europe (6, 11). The phenotype frequencies found in these studies do not deviate significantly from the Danish ones. A very limited investigation on Esquimos published by *Grubb* (6) suggests that a racial variation in gene frequencies may be found.

Summary

An extensive family study and twin investigation has confirmed the hereditary nature of the newly identified, human serum group, *the Gm system*. The technique is described which allows a classification of normal individuals, based on the presence (or absence) of a special kind of inhibitor in the serum. The presence of this factor seems to be determined by a single gene, capable of manifestation in the heterozygous state. The frequency of this gene in Denmark is estimated to be 0.334.

The Gm serum group was not found to be correlated with sex, the AB0, MNS, Rh, P, Lewis, Kell, Lutheran or Duffy blood group systems, nor with the Hp group.

The special conditions occuring in early childhood are mentioned.

The value of the Gm serum group in the various aspects of genetic work is discussed.

The necessity of further studies, especially of children during their first years of life, is stressed.

Zusammenfassung

Eine ausgedehnte Familien- und Zwillingsuntersuchung bestätigte die erbliche Natur der neu identifizierten menschlichen Serumgruppen, des Gm-Systems. Es wird eine Untersuchungsmethodik beschrieben, die eine Klassifizierung normaler Individuen danach, ob ein spezieller Inhibitor im Serum vorhanden ist oder nicht, gestattet. Die Anwesenheit dieses Faktors ist offenbar durch ein einziges Gen verursacht, das sich in heterozygotem Zustand manifestieren kann. Die Häufigkeit dieses Gens in Dänemark wird auf 0,334 geschätzt.

Es fand sich keine Korrelation der Gm-Serumgruppen mit dem Geschlecht, den AB0-, MNS-, Rh-, P-, Lewis-, Lutheran- oder Duffy Blutfaktoren und ebenfalls nicht mit der Hp-Gruppe.

Die speziellen Verhältnisse in der frühen Kindheit werden erwähnt, und es wird der Wert der Gm-Serumgruppen unter den verschiedenen Aspekten der genetischen Arbeit diskutiert.

Es wird betont, daß es notwendig ist, weitere Untersuchungen besonders an Kindern während der ersten Lebensjahre durchzuführen.

Resumé

Une étude approfondie dans différentes familles et chez des jumeaux a permis de confirmer la nature héréditaire du groupe sanguin Gm, récemment identifié, dans le sérum humain. La technique qui permet une classification des sujets normaux, basée sur la présence (ou l'absence) d'un inhibiteur d'un type spécial dans le sérum est décrite. La présence de ce facteur semble être due à un seul gène, capable de se manifester dans l'état hétérozygote. La fréquence de ce gène au Danemark est estimée à 0,334.

Il n'a pas été possible de mettre en évidence une corrélation avec le sexe, les groupes sanguins AB0, MNS, Rh, P, Lewis, Kell, Lutheran ou Duffy, ni avec le groupe Hp.

Les conditions spéciales se présentant chez le jeune enfant sont mentionnées.

L'importance du groupe Gm dans les différents aspects du point de vue des recherches génétiques est discutée.

On souligne la nécessité de recherches complémentaires, surtout en ce qui concerne les enfants pendant les premières années de leur vie.

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APPENDIX

List of all families with both parents and at least one child tested.

Key to appendix:

Column 1. Family number.

2. Sex (M = male, F = female). Brackets indicate twins.

3. Year of birth.

4–11. Blood group systems.

4. AB0. Anti-sera used: anti-A, -B, α_1.

5. MNS. Anti-sera used: anti-M, -N, -S.

6. Rhesus. Anti-sera used: anti-C, -D, -E, -c; anti-e only in cases with presence of E.

Key to phenotypes:		Most likely genotype:
rr	= C—D—E—c+e+	cde/cde
R_0r	= C—D+E—c+e+	cDe/cde
R″r	= C—D—E+c+e+	cdE/cde
R_2R_2	= C—D+E+c+e—	cDE/cDE
R_2r	= C—D+E+c+e+	cDE/cde
R_0R_2	= C—D+E+c+e+	cDe/cDE
R′r	= C+D—E—c+e+	Cde/cde
R_1r	= C+D+E—c+e+	CDe/cde
R_1R_2	= C+D+E+c+e+	CDe/cDE
$R_1R″$	= C+D+E+c+e+	CDe/cdE
R_1R_1	= C+D+E—c—e+	CDe/CDe
$R_1R′$	= C+D+E—c—e+	CDe/Cde
R_1R_Z	= C+D+E+c—e+	CDe/CDE

7. P = P phenotype, P+ or P—.

8. Le(a) = Lewis phenotype Le(a+) or Le(a—).

9. K   = Kell phenotype, K+ or K—.

10. Lutheran phenotype, Lu(a+) or Lu(a—).

11. Fy(a) = Duffy phenotype, Fy(a+) or Fy(a—).

12–13. Serum group systems.

12. Gm(a) = Gm serum group, Gm(a+) or Gm(a—).

13. Hp = Haptoglobin group, Hp 1–1, Hp 2–1, Hp 2–2, u = undeveloped.

Within the families the parents are set out first.

No.	Sex	Y. of b.	AB0	MNS	Rh	P	Le(a)	K	Fy(a)	Gm(a)	Hp
G 1	M	1882	A_1	MS	R_1r	+	—	—	+	+	2–2
	F	1881	A_1	Ns	R_1R_1	+	—	—	+	+	1–1
	F	1912	A_1	MNS	R_1r	—	—	—	+	+	2–1
	M	1916	A_1	MNS	R_1r	+	—	—	—	+	2–1
	M	1918	A_1	MNS	R_1R_1	—	—	—	+	+	2–1
	M	1922	A_1	MNS	R_1R_1	+	—	—	—	+	2–1
G 2	M	1904	A_1	MS	rr	+	—	—	—	+	2–1
	F	1905	B	Ms	R_2r	—	—	+	+	—	2–2
	F	1937	A_1B	MS	R_2r	—	—	—	—	+	2–1
	M	1939	A_1B	MS	R_2r	+	—	—	—	+	2–2
	F	1941	A_1	MS	R_2r	+	—	—	—	+	2–1
	F	1942	A_1B	MS	rr	+	—	—	—	+	2–1
	M	1944	A_1	MS	rr	—	—	—	—	+	2–2
G 3	M	1918	B	MNS	rr	+	—	—	—	—	2–1
	F	1917	B	MNs	R_1r	—	—	—	+	+	2–2
	M	1945	0	MNs	R_1r	+	—	—	—	+	2–2
	M	1948	B	NS	rr	+	—	—	—	+	2–1
G 4	M	1886	0	MNs	R_1r	+	—	—	—	+	2–1
	F	1892	A_1	Ns	rr	+	—	—	+	+	2–2
	M	1919	A_1	Ns	R_1r	+	—	—	—	+	2–1
	F	1920	0	Ns	rr	+	+	—	—	+	2–1
	M	1921	0	Ns	rr	+	+	—	+	+	2–1
	M	1924	A_1	MNs	R_1r	—	+	—	—	+	2–2
	F	1925	A_1	Ns	R_1r	+	—	—	—	+	2–1
	M	1926	0	MNs	rr	—	+	—	+	+	2–1
	M	1930	A_1	MNs	rr	+	—	—	+	+	2–2
	F	1932	A_1	Ns	rr	+		—	+	+	2–2
	M	1939	0	Ns	rr	—	—	—	—	+	2–1
G 5	M	1904	0	MS	R_1r	+	—	—		+	2–1
	F	1905	0	Ms	R_1R_1	+	—	—	+	+	2–1
	F	1932	0	Ms	R_1r	(+)	—	—		+	2–2
	M	1936	0	Ms	R_1R_1	—	+	—	+	—	1–1
	M	1940	0	MS	R_1r	+	+	—	+	—	2–1
G 6	M	1891	0	MNS	R_2r	+	—	—	+		2–1
	F	1892	A_1	Ms	R_1R_1	+	—	—	+		2–1
	F	1922	0	MNS	R_1r	+	—	—	+	+	2–2
G 7	M	1903	0	MNs	R_1R_1	+	+	—	—	—	1–1
	F	1902	A_1	MS	R_1R_1	+	+	—	—	—	2–1
	F	1931	A_1	Ms	R_1R_1	+	+	—	—		2–1
	F	1935	A_1	MS	R_1R_1	+	+	—	—	—	1–1
G 8	M	1885	0	MNS	rr	—	—	—	+	—	2–2
	F	1888	0	Ns	rr	—	+	—	—	+	1–1
	M	1916	0	NS	rr	—	+	—	+	+	2–1
	F	1920	0	MNS	rr	—	—	—	—	+	2–1
G 9	M	1886	A_1	Ns	R_1R_2	+	+	—	+		2–1
	F	1889	0	MS	R_1r	+	—	—	—		2–2
	F	1917	A_1	MNS	R_1r	+	+	—	—		2–2
	M⎱	1920	0	MNS	R_2r	+	+	—	—		2–2
	F⎰	1920	0	MNS	R_1r	+	+	—	+		2–2
G 10	M	1898	A_1	Ns	rr	—	—	—	—	—	2–1
	F	1905	0	Ns	R_1r	+	—	+	+	+	2–1
	F⎱	1941	0	Ns	R_1r	—	—	—	+	—	1–1
	F⎰	1941	0	Ns	R_1r	—	—	—	+	—	1–1

No.	Sex	Y. of b.	AB0	MNS	Rh	P	Le(a)	K	Fy(a)	Gm(a)	Hp
G 11	M	1916	0	MNs	rr	+	—	—	+	—	2–1
	F	1917	0	Ms	R_1r	+	—	—	+	—	2–1
	M	1942	0	Ms	R_1r	+	—	—	+	—	1–1
	F	1946	0	MNs	rr	—	—	—	+	—	1–1
G 12	M	1918	A_1	NS	R_1r	+	—	—	+	+	2–1
	F	1920	A_2	NS	R_1R_2	+	—	—	+	—	2–1
	M	1944	A_2	NS	R_1r	+	—	—	+	+	2–1
	F	1949	A_2	NS	R_1R_1	+	—	—	+	+	2–1
G 13	M	.	A_1	MNS	R_1R_2	+	—	—	+	—	1–1
	F	1905	A_1	MNS	rr	+	—	—	—	+	2–1
	F	1934	A_1	MS	R_1r	+	—	—	+	+	2–1
	F	1936	A_1	MNS	R_2r	—	—	—	+	—	2–1
	F	1942	A_1	MNS	R_2r	—	—	—	+	—	1–1
G 14	M	.	A_2B	MS	R_1R_1	+	—	—	+	+	2–1
	F	.	A_1	MS	R_2r	+	—	—	—	+	2–1
	M	.	A_1B	Ms	.	—	—	—	—	+	2–1
	M	.	B	Ms	R_1r	+	—	—	+	+	2–2
G 15	M	.	A							—	2–2
	F	1906	A							—	2–2
	F	1934	A							—	2–2
	F	1935	0							—	2–2
	F	1937	0							—	2–2
	M	1938	A							—	2–2
	M	1940	A							—	2–2
	F	1942	0							—	2–2
	F	1944	0							—	2–2
G 16	M	.	0	N		+				—	2–2
	F	1913	B	MN		—				+	1–1
	F	1931	0							+	2–1
	F	1937	0							—	2–1
	F	1939	B							—	2–1
G 17	M	1919	0	N	rr	+	—	—		+	2–2
	F	.	A							—	2–1
	F	.	A							—	2–1
	F	.	A							+	2–1
	F	.	A							—	2–1
	F	.	A							+	2–1
G 18	M	.	0							+	2–2
	F	.	A_2							—	2–1
	M	.	0							—	2–2
	F	.	0							—	2–2
G 19	M	.	0	MNs	rr	+	+	—		+	2–2
	F	.	0	MNS	rr	+	—	—		+	2–2
	M	1945	0		rr					+	2–2
	F	1946	0		rr					+	2–2
	F	1949	0		rr					+	2–2
G 20	M	.	0	Ms	R_1R_1	—	—	—		—	2–2
	F	.	0							—	2–2
	M	.	0							—	2–2
	F	.	0							—	2–2
	M	.	0							—	2–2
	F	.	0							—	2–2

No.	Sex	Y. of b.	ABO	MNS	Rh	P	Le(a)	K	Fy(a)	Gm(a)	Hp
G 21	M	.	0							—	2–1
	F	.	A							—	2–1
	F	.	A							—	2–1
	M	.	A							—	2–2
	M	.	A							—	2–2
G 22	M	.	A							+	2–1
	F	.	0							.	2–2
	F	.	A							—	2–2
	F	.	A							—	2–1
	F	.	A							—	2–2
	F	.	A							–	2–1
G 23	M	.	0							–	2–1
	F	.	0							—	1–1
	M	.	0							–	2–1
	F	.	0							–	1–1
G 24	M	.	A							–	2–2
	F	.	B							–	1–1
	M	.	0							–	2–1
	M	.	0							.	2–1
	F	.	B								2–1
G 25	M	.	B							–	2–2
	F	.	0							—	2–1
	F	.	0							—	2–2
	F	.	0							—	2–2
	F	.	B							—	2–1
	M	.	0							–	2–2
	M	.	0								2–1
G 26	M	.	0							—	2–2
	F	.	0							–	2–1
	F	.	0							–	2–2
	M	.	0							–	2–2
G 27	M	.	A							—	1–1
	F	.	A							–	2–2
	M	.	0							–	2–1
	M	.	A							–	2–1
G 28	M	.	0							—	2–1
	F	.	0							—	2–1
	M	.	0							—	1–1
	F	.	0							—	2–1
	F	.	0							—	2–1
	M	.	0							—	2–1
	M	.	0							—	2–1
	F	.	0							—	2–1
	F	.	0							—	2–1
G 29	M	.	0							–	2–1
	F	.	AB							–	2–2
	F	.	A							–	2–1
	M	.	A							–	2–2
	F	.	A							...	2–2
	M	.	B							+	2–2
	F	.	A							–	2–1
	F	.	A							–	2–1
	F	.	B							–	2–1
	F	.	A							–	2–2

No.	Sex	Y. of b.	AB0	MNS	Rh	P	Le(a)	K	Fy(a)	Gm(a)	Hp
G 30	M	.	A							+	2–1
	F	.	A							—	2–1
	M	.	0							+	2–2
	F	.	A							+	2–1
	F	.	A							+	2–2
G 31	M	.	0							+	2–1
	F	.	0							+	2–2
	F	.	0							+	2–2
	F	.	0							.	2–2
	M	.	0							—	2–2
G 32	M	1911	0	MNs	rr	+	—	—	+	+	2–1
	F	1917	A_2	MNs	rr	+	—	—	—	—	1–1
	F	1940	0	Ms	rr	+	—	—	+	—	2–1
	F	1942	0	MNs	rr	+	+	—	+	+	1–1
	F	1944	A_2	MNs	rr	+	+	—	+	+	1–1
G 33	M	1913	A_1	Ms	rr	+	—	—	+	+	2–2
	F	1917	B	MS	R_1R_1	+	—	—	+	—	2–1
	M	1940	A_1	Ms	R_1r	(+)	—	—	+	+	2–2
	M	1942	A_1B	MS	R_1r	+	—	—	+	+	2–2
G 34	M	1911	B	MNs	R_2r	+	—	—	+	—	2–2
	F	1912	0	MNS	R_1R_1	+	—	—	—	+	2–2
	F	1940	0	Ns	R_1r	+	—	—	—	—	2–2
	F	1943	B	Ns	R_1R_2	+	+	—	+	+	2–2
	M	1946	B	MS	R_1R_2	+	—	—	+	+	2–2
G 35	M	1916	0	NS	rr .	+	—	—	+	—	2–1
	F	1920	A_1	MNs	R_1R_2	+	—	—	—	—	2–2
	F	1942	A_1	MNs	R_2r	+	—	—	—	—	2–1
G 36	M	1916	0	MNs	R_1r	+	—	—	—	—	2–2
	F	1920	0	Ns	R_1r	—	—	—	—	+	2–1
	M	1947	0	MNs	R_1r	—	—	—	—	+	2–1
	M	1950	0	Ns	R_1R_1	+	—	—	—	+	2–2
G 37	M	1905	B	MS	R_2r	+	—	—	+	+	2–2
	F	1913	A_2	NS	rr	+	—	—	+	—	2–2
	F	1937	0	MNS	R_2r	+	—	—	+	+	2–2
	M	1940	A_2B	MNS	R_2r	—	—	—	—	+	2–2
G 38	M	1908	A_1	MNs	R_1r	+	—	—	—	—	2–2
	F	1916	0	MS	R_1R_1	+	—	—	+	+	1–1
	F	1937	A_1	Ms	R_1r	+	—	—	—	+	2–1
	F	1940	A_1	MNs	R_1r	+	—	—	—	+	2–1
G 39	M	1894	B	MNS	R_2r	—		—	+	—	2–2
	F	1890	A_1B	MNs	R_2r	+		—	+	+	2–1
	M	1921	A_1B	MNs	R_2R_2	+	+	—	+	+	2–1
	M	1923	A_1B	MNS	R_2r	—	+	—	+	+	2–2
	M	1926	A_1B	MNs	R_2r	—	—	—	+	+	2–1
G 40	M	1906	0	MNS	R_1R_1	+	+	—	—	—	2–2
	F	1906	B	MNs	R_1R_2	—	—	—	+	+	1–1
	M	1939	B	MNS	R_1R_1	—	+	—	+	+	2–1
	F	1945	B	Ns	R_1R_1	—	.	—	.	.	2 1
G 41	M	1905	B	Ns	R_1r	+	—	—	—	+	2–2
	F	1907	0	MNs	rr	+	—	—	—	+	2–1
	M	1938	0	MNs	rr	+	—	—	—	+	2–2
	M	1940	0	Ns	rr	+	—	—	—	+	2–1

No.	Sex	Y. of b.	AB0	MNS	Rh	P	Le(a)	K	Fy(a)	Gm(a)	Hp
G 42	M	1902	A_2B	MS	rr	+	—	—	—	+	2–2
	F	1908	0	Ns	R_1R_2	+	—	—	+	—	2–1
	M	1933	B	MNS	R_2r	+	—	—	+	—	2–1
	F	1936	B	MNS	R_2r	+	—	—	+	—	2–1
	F	1940	B	MNs	R_1r	+	—	—	+	+	2–2
	M	1942	A*	MNs	R_2r	+	—	—	—	—	2–1
G 43	M	1916	0	MNS	R_1r	+	—	—	+	+	2–2
	F	1918	0	Ns	R_1r	—	—	—	+	+	2–1
	F	1943	0	MNs	R_1r	+	+	—	+	+	2–1
	M	1946	0	NS	R_1R_1	+	+	—	+	+	2–1
G 44	M	1921	0	Ms	R_1r	—	—	—	+	+	2–2
	F	1921	A_2	MNS	R_2r	—	—	—	+	+	2–2
	F	1947	0	MS	R_2r	—	—	—	+	+	2–2
	F	1950	A_2	MS	R_2r	—	—	—	—	+	2–2
G 45	M	1905	0	Ns	R_1r	+	—	—	+	+	2–2
	F	1911	B	MS	R_1R_2	+	—	—	+	+	2–2
	M	1934	B	MNS	R_2r	+	—	—	+	+	2–2
	M	1938	0	MNS	R_1r	+	—	—	+	+	2–2
G 46	M	1911	0	Ms	R_1r	+	—	—	—	+	1–1
	F	1915	A_2	MNS	R_1R_1	+	+	—	+	+	1–1
	M	1939	0	MNs	R_1r	+	—	—	—	+	1–1
	M	1946	0	MNs	R_1r	+	—	—	+	+	1–1
G 47	M	1907	A_1	Ns	R_1R_1	+	—	—	+	—	2–1
	F	1907	A_1	Ms	R_1R_2	+	+	—	+	—	1–1
	F	1935	A_1	MNs	R_1R_1	+	—	—	+	—	1–1
	F⎫	1936	0	MNs	R_1R_2	+	—	—	—	—	1–1
	F⎭	1936	A_1	MNs	R_1R_2	+	—	—	+	—	1–1
	M	1941	A_1	MNs	R_1R_2	+	—	—	—	—	1–1
G 48	M	1914	A_1	MNS	R_2r	—	—	—	+	+	2–1
	F	1925	A_2B	Ms	rr	+	—	—	+	+	2–2
	M	1945	A_1	MNs	R_2r	+	—	—	+	+	2–1
	F	1946	A_1B	MS	rr	+	—	—	+	+	2–2
G 49	M	1917	A_2	MNS	R_2r	+	—	—	+	+	2–2
	F	1918	A_1	MNS	R_1r	+	—	—	+	+	2–1
	M	1944	A_1	Ns	R_2r	+	+	—	+	—	2–2
	M	1947	0	Ns	R_1r	+	—	—	+	—	2–2
G 50	M	1915	A_2	MS	rr	+		—	—	—	2–2
	F	1915	A_1B	Ms	R_1r	+	—	—	+	+	2–1
	M	1944	B	MS	rr	+	—	—	+	—	2–1
	M	1945	A_1	MS	R_1r	+	—	—	+	—	2–1
	M	1946	A_1	MS	R_1r	—	—	—	—	—	2–1
	F	1953	B	MS	rr	+	—	—	+	—	2–2
G 51	M	1913	A_1	Ms	R_2r	+	—	—	—	—	2–1
	F	1917	0	Ns	R_1r	+	—	—	—	+	2–1
	M	1942	A_1	MNs	R_1R_2	+	—	—	—	—	2–2
	F	1946	0	MNs	R_2r	+	—	—	—	—	2–1
G 52	M	1915	B	Ns	R_1R_2	—	+	—	—	—	2–1
	F	1920	A_1	Ns	R_0r	+	+	—	+	+	2–1
	M	1947	0	Ns	R_2r	+	+	—	—	+	2–1
	F	1948	B	Ns	R_2r	+	+	—	—	+	2–2

* i.e. intermediate between A_1 and A_2

No.	Sex	Y. of b.	AB0	MNS	Rh	P	Le(a)	K	Fy(a)	Gm(a)	Hp
G 53	M	1896	0	Ns	rr	±	—	—	+	+	1–1
	F	1902	0	Ns	R_1R_2	—	—	—	—	+	1–1
	F	1932	0	Ns	R_1r	+	—	—	—	+	1–1
	F	1938	0	Ns	R_1r	+	—	—	—	+	1–1
G 54	M	1904	0	Ms	R_1R_1	—	+	—	—	+	1–1
	F	1905	A_1	MNs	R_1r	+	—	—	—	—	2–1
	F⎫	1937	A_1	MNs	R_1r	+	—	—	—	+	2–1
	F⎭	1937	A_1	Ms	R_1r	—	—	—	—	+	2–1
G 55	M	1916	0	MS	R_1R_2	+	—	—	+	—	2–1
	F	1921	A_1	MNS	rr	+	—	—	+	+	2–1
	F	1945	A_1	MNS	R_2r	—	—	—	+	+	2–1
G 56	M	1901	0	MS	R_1R_2	+	—	—	+	—	2–1
	F	1910	0	NS	R_1R_2	+	+	—	—	+	1–1
	M⎫	1937	0	MNS	.	+	—	—	—	—	2–1
	M⎭	1937	0	MNS	R_1R_2	±	—	—	—	+	2–1
G 57	M	1925	0	MS	R_0r	+	—	—	—	+	2–1
	F	1926	0	MS	R_1R_1	+	+	—	+	+	2–1
	M	1947	0	Ms	R_1r	+	—	—	+	+	2–2
G 58	M	1910	A_2	MNs	rr	+	+	—	+	—	2–2
	F	1910	0	Ns	R_1R_1	+	—	—	—	+	2–2
	F	1940	0	Ns	R_1r	+	+	—	+	+	2–2
	F	1946	A_2	MNs	R_1r	+	—	—	+	+	u.
G 59	M	1919	0	MS	R_1r	+	+	+	—	—	2–1
	F	1920	A_2B	MNS	R_1r	—	—	—	—	—	2–2
	F	1940	B	MS	R_1r	+	—	—	—	—	2–1
	M	1941	B	MNs	rr	+	—	+	—	—	2–1
	M	1943	A_2	MNS	rr	—	—	+	—	—	2–2
	F	1946	B	MNS	rr	+	—	—	—	—	2–1
G 60	M	1914	A_1	MS	rr	—	—	—	+	—	2–2
	F	1909	A_1	Ns	R_2r	+	—	—	+	+	1–1
	F	1940	A_1	MNS	R_2r	—	—	—	+	+	2–1
	M	1944	A_1	MNS	rr	—	—	—	+	+	2–1
G 61	M	1914	0	MS	rr	—	—	—	—	—	2–1
	F	1915	0	MS	R_1r	+	—	—	—	+	2–2
	M	1940	0	MS	R_1r	+	—	—	—	+	2–1
	M	1943	0	MS	R_1r	+	—	—	—	+	2–1
G 62	M	1911	A_1	Ns	R_1R_1	+	+	—	—	+	2–1
	F	1909	A_1	MNS	R_1r	+	—	—	+	+	2–2
	F	1937	A_1	MNS	R_1R_1	+	+	—	+	+	2–2
	F	1942	A_1	MNS	R_1R_1	+	—	—	+	÷	2–2
G 63	M	1911	B	MNs	rr	+	+	—	÷	+	2–2
	F	1909	A_2	MNS	R_1R_1	+	—	—	+	+	2–1
	M	1939	B	Ns	R_1r	+	+	—	—	+	2–1
	M	1942	B	MNs	R_1r	+	+	—	+	÷	2–2
G 64	M	1917	A_1	MNs	R_1R_2	+	—	—	+	—	1–1
	F	1919	0	MNs	R_1R_1	÷	—	—	—	—	2–2
	M	1942	A_1	Ms	R_1R_2	÷	—	—	—·	—	2–1
	M	1946	A_1	Ns	R_1R_2	+	—	—	—	—	2–1
G 65	M	1914	0	MNS	R_2r	÷	—	—	—	—	2–1
	F	1912	A_1	MS	R_1r	—	—	—	+	—	2–2
	F	1940	A_1	MNS	R_1R_2	÷	—	—	÷	—	2–1
	M	1943	0	MS	R_1R_2	—	—	—	+	—	2–1

No.	Sex	Y. of b.	AB0	MNS	Rh	P	Le(a)	K	Fy(a)	Gm(a)	Hp
G 66	M	1922	A_1	MNS	R_1r	+	—	—	+	+	2–2
	F	1921	A_1	Ms	R_1R_1	+	—	—	+	+	2–2
	F	1945	0	MNs	R_1R_1	+	—	—	+	+	2–2
	F	1947	0	MS	R_1r	+	—	—	—	+	2–2
G 67	M	1908	A_1B	MNs	R_0r	+	+	—	+	+	2–1
	F	1913	0	Ns	R_2r	+	—	—	+	—	1–1
	M	1937	B	Ns	R_2r	+	—	—	+	—	2–1
	F	1939	B	MNs	R_2r	+	—	—	+	+	2–1
	F	1950	B	Ns	R_0r	+	+	—	+	+	2–1
G 68	M	1919	0	MNs	R_1R_1		+	—	+	+	2–1
	F	1920	A_1	MS	R_1r	+	—	—	+	+	2–1
	F	1940	A_1	MNS	R_1r	+	+	—	+	+	1–1
	F	1948	A_1	MNS	R_1r	—	+	—	—	+	2–2
G 69	M	1913	B	MNS	R_1r	+	+	—	—	+	2–1
	F	1913	0	Ms	R_1r	—	—	—	+	—	2–1
	M	1944	B	MNs	R_1R_1	+	—	—	—	+	2–1
	F	1945	B	MNs	rr	+	—	—	+	—	2–2
	M	1951	B	MS	R_1R_1	+	—	—	—	+	2–1
G 70	M	1916	0	MNs	R_2r	—	—	—	—	+	2–1
	F	1920	0	NS	R_2r	+	—	—	+	+	2–2
	M	1943	0	MNs	R_2r	+	—	—	—	+	2–1
	M	1946	0	NS	rr	+	—	—	—	+	2–2
G 71	M	1922	A_1	MNs	R_1r	+	—	—	+	—	2–1
	F	1922	A_1	MNS	R_1R_2	+	—	—	+	+	2–2
	M	1946	A_1	MNS	R_1R_2	+	—	—	+	+	2–1
	M	1947	A_1	MS	R_1R_2	+	—	—	—	—	2–2
G 72	M	1908	0	Ms	R_1r	—	+	—	+	+	2–1
	F	1908	A_1	Ms	rr	+	+	—	+	—	2–2
	F	1935	0	Ms	R_1r	—	+	—	+	+	2–2
	M	1944	A_1	Ms	R_1r	—	+	—	+	+	2–1
G 73	M	1912	0	MS	R_0r	—	—	—	—	—	2–2
	F	1911	B	MS	R_1R_1	—	—	—	+	+	2–1
	M	1944	0	MS	R_1r	—	—	—	+	—	2–1
	M	1946	0	MS	R_1r	—	—	—	—	—	u.
G 74	M	1921	A_1	MNs	R_1R_2	—	—	—	—	+	2–2
	F	1921	A_1	MNs	R_1r	+	—	—	—	+	2–1
	M	1945	A_1	MNs	R_1r	+	—	—	—	+	2–2
	F	1950	A_1	MNs	R_1R_1	·	..	—	...	..	2–2
G 75	M	1916	0	Ns	R_1r	+	+	—	+	—	1–1
	F	1917	A_1	NS	R_1r	—	—	—	—	—	2–2
	M	1941	0	Ns	R_1r	+	—	—	—	—	2–1
	F	1943	A_1	Ns	rr	+	—	—	+	—	2–1
	M	1947	A_1	Ns	R_1r	+	—	—	—	—	2–1
G 76	M	1919	A_1	MS	R_1r	+	—	—	+	+	2–1
	F	1918	A_2	MS	R_1r	+	—	—	+	—	1–1
	M	1943	A_1	Ms	R_1r	+	+	—	+	+	1–1
	M	1944	A_2	MS	R_1r	+	—	—	+	+	2–1
G 77	M	1919	A_2B	Ns	rr	—	—	—	+	—	2–1
	F	1918	0	MNS	R_1R_2	—	—	—	—	+	2–1
	M	1944	A_2	Ns	R_2r	—	—	—	+	+	2–1
	M	1947	B	MNS	R_2r	—	—	—	—	+	2–1

No.	Sex	Y. of b.	AB0	MNS	Rh	P	Le(a)	K	Fy(a)	Gm(a)	Hp
G 78	M	1918	A_2	Ns	R_1r	+	+	—	+	—	2–1
	F	1918	0	Ns	R_1R_2	+	—	—	+	+	2–2
	F	1945	0	Ns	R_1R_1	+	+	—	+	+	2–1
	F	1950	0	Ns	R_1R_2	—	—	—	+	—	2–1
G 79	M	1919	A_2	MNs	R_1R_1	—	—	—	+	+	2–1
	F	1918	A_1	MNS	R_2r	+	—	—	+	+	2–1
	M	1943	A_1	MNS	R_1R_2	+	+	—	+	+	2–1
G 80	M	1903	0	MNs	rr	+	+	—	—	+	2–1
	F	1911	B	MNs	rr	+	—	—	—	—	2–1
	F	1936	0	MNs	rr	—	—	—	—	—	2–1
	F	1945	0	Ms	rr	—	+	—	—	+	2–1
	M	1948	0	Ns	rr	+	—	—	—	+	2–2
G 81	M	1905	0	Ms	R_1r	—	—	—	—	—	2–1
	F	1910	A_2	MS	R_1R_2	+	+	—	—	+	1–1
	M	1940	0	MS	R_1r	—	+	—	—	—	1–1
	M	1945	0	MS	R_2r	—	—	—	—	+	2–1
	M	1947	A_2	MS	R_2r	—	—	—	—	—	2–1
G 82	M	1905	A_1	MNS	R_1r	+	—	—	+	—	2–2
	F	1908	A_2	MNS	R_1R_2	+	+	—	+	—	1–1
	F	1937	A_1	MNS	R_1R_1	+	+	—	—	—	2–1
	F	1939	0	Ns	R_1R_2	+	—	—	+	—	2–1
	F	1941	A_1	MNS	R_1R_2	+	—	—	—	—	2–1
	F	1943	A_2	MS	R_1R_2	+	—	—	+	—	2–1
G 83	M	1915	A_2	MS	R_1r	—	—	—	+	—	2–2
	F	1921	A_1	MNS	R_1R_2	+	—	—	+	—	2–1
	F	1945	A_1	MNS	R_1r	—	—	—	+	—	2–1
	F	1949	A_1	MNs	R_1R_2	—	—	—	+	—	2–1
G 84	M	1909	A_2	MNs	R_2r	—	—	—	—	—	2–1
	F	1911	0	MNs	R_1R_1	+	—	—	—	+	2–2
	M	1940	0	MNs	R_1R_2	(+)	—	—	—	—	2–1
	M	1941	A_2	MNs	R_1R_2	+	—	—	—	+	2–1
	F	1945	A_2	Ns	R_1r	+	—	—	—	—	2–2
G 85	M	1915	A_1	MNS	R_1R_1	—	+	—	+	+	2–2
	F	1915	0	MNS	R_1R_2	—	—	—	+	—	1–1
	F	1941	0	MS	R_1R_1	—	—	—	+	+	2–1
G 86	M	1911	B	MNs	rr	+	+	—	—	+	2–1
	F	1910	0	MNS	R_1r	—	—	—	—		1–1
	M	1939	0	Ns	R_1r	+	—	—	—	+	1–1
	M	1941	B	MS	R_1r	+	—	—	—	+	1–1
G 87	M	1916	B	MNs	R_1r	+	+	—	+	—	2–2
	F	1916	A_2	MS	R_1R_2	+	+	—	+	+	2–1
	F	1939	B	MS	R_2r	+	+	—	—	—	2–1
	F	1941	B	MS	R_1R_2	+	+	—	+	—	2–2
	M	1945	B	MS	R_2r	+	+	—	+	+	2–2
G 88	M	1918	0	Ns	R_1r	+	—	—	+	—	2–1
	F	1917	0	Ns	R_1R_2	—	—	—	+	+	2–2
	F	1944	0	Ns	R_1R_1	+	—	—	+	—	2–2
	M	1947	0	Ns	R_1r	+	—	—	+	—	2–2
G 89	M	1910	B	MNs	R_2r	+	—	+	+	—	2–1
	F	1912	A_1	MNS	R_1r	+	—	+	+	+	2–1
	F	1941	0	MNs	R_1r	+	—	+	+	—	u.
	M	1944	A_1B	MNS	rr	—	+	—	+	—	1–1

No.	Sex	Y. of b.	AB0	MNS	Rh	P	Le(a)	K	Fy(a)	Gm(a)	Hp
G 90	M	1913	B	MNS	rr	+	—	—	—	+	1–1
	F	1913	A_2	Ns	rr	+	—	—	+	—	1–1
	F	1943	A_2B	Ns	rr	—	—	—	+	+	1–1
	M	1947	A_2B	MNS	rr	—	—	—	+	+	1–1
G 91	M	1916	0	MS	R_1r	+	—	—	—	—	2–2
	F	1914	A_1	MS	R_1r	+	—	—	+	+	2–1
	F	1942	0	Ms	R_1r	+	—	—	+	—	2–1
	F	1943	0	MS	R_1r	—	—	—	—	+	2–2
	M	1945	0	MS	rr	—	—	—	—	—	2–2
G 92	M	1921	A_1	MNS	R_1R_1	+	+	—	+	+	1–1
	F	1924	0	NS	R_1R_2	+	—	—	+	+	2–2
	F	1944	A_1	MNS	R_1R_2	+	—	—	+	+	2–1
	M	1948	A_1	MNS	R_1R_2	+	—	—	+	+	2–1
G 93	M	1915	A_1	MNS	R_1R_2	+	—	—	+	+	2–1
	F	1920	B	MS	rr	+	—	—	—	+	2–2
	M	1945	A_1	Ms	R_2r	+	—	—	+	—	2–1
	F	1946	A_2	MNS	R_1r	+	—	—	+	+	2–1
	F	1949	A_2	MNS	R_1r	+	—	—	+	+	2–2
G 94	M	1918	0	MS	R_1r	—	+	—	—	+	2–1
	F	1914	B	Ms	R_2r	—	—	—	—	—	2–2
	F	1943	0	MS	R_2r	+	—	—	—	+	2–1
	M	1948	0	MS	R_2r	—	—	—	—	—	2–2
G 95	M	1920	B	Ms	R_2r	+	+	—	+	—	2–2
	F	1924	A_2	MNS	R_2r	—	+	—	+	+	2–1
	M	1947	A_2B	MNS	R_2R_2	+	+	—	—	—	2–2
	M	1951	A_2	MNS	R_2R_2	—	+	—	+	—	2–1
G 96	M	1904	A_1	MS	R_2R_2	+	+	—	+	—	2–1
	F	1908	A_2	Ms	R_1r	—	+	—	+	—	2–1
	M	1934	A_2	Ms	R_2r	+	+	—	+	—	2–1
	F	1937	A_1	MS	R_1R_2	+	—	—	+	—	2–1
G 97	M	1906	0	MNS	R_1r	+	—	—	—	—	1–1
	F	1915	0	MNs	R_1R_2	—	—	+	+	+	2–1
	M	1939	0	MS	R_1R_1	+	—	+	—	+	2–1
	M	1942	0	MNs	R_2r	+	—	+	+	+	2–1
G 98	M	1918	A_1	MNS	rr	+	—	—	+	—	2–2
	F	1920	A_1	Ns	R_1R_1	+	+	—	+	—	2–1
	F	1943	A_1	MNS	R_1r	+	—	—	+	—	2–2
	M	1947	A_1	MNS	R_1r	+	—	—	—	—	2–2
G 99	M	1918	A_1	MNs	rr	+	—	—	—	—	2–1
	F	1918	A_2	Ns	rr	—	+	—	+	—	2–1
	M	1940	A_1	Ns	rr	+	—	—	—	—	2–1
	M	1947	A_1	Ns	rr	+	+	—	—	—	1–1
G 100	M	1918	B	MS	$R'r$	+	—	—	+	+	2–2
	F	1926	A_1	Ms	R_2r	+	—	—	—	+	2–1
	M	1944	A_2B	MS	rr	+	+	—	+	+	u.
	M	1949	A_1	MS	$R'r$	+	—	—	—	+	u.
	M	1951	A_1	MS	$R'R_2$	+	—	—	—	+	2–2
G 101	M	1920	0	MS	$R''r$	+	+	—	+	+	2–1
	F	1928	A_1	Ms	rr	+	—	+	—	—	2–1
	F	1945	A_1	MS	$R''r$	+	+	—	—	—	1–1
	F	1947	A_1	Ms	$R''r$	+	+	+	+	—	2–1
	F	1948	A_1	Ms	rr	+	+	—	+	+	2–2

No.	Sex	Y. of b.	AB0	MNS	Rh	P	Le(a)	K	Fy(a)	Gm(a)	Hp
G 102	M	1918	0	MNs	rr	+ .	—	—	+	+	2–1
	F	1918	B	MNs	rr	—	—	—	+	—	2–2
	M	1941	0	Ns	rr	+	—	—	+	—	2–1
	M	1946	0	MNs	rr	+	—	—	+	+	u.
G 103	M	1914	0	Ns	rr	+	—	—	+	+	2–1
	F	1914	A_1	Ms	R_1r	+	—	—	+	+	1–1
	F	1940	A_1	MNs	R_1r	+	+	—	+	+	2–1
	F	1942	0	MNs	rr	+	+	—	+	+	1–1
	F	1944	A_1	MNs	rr	+	—	—	+	+	2–1
G 104	M	1903	0	MS	R_1r	—	—	—	—	—	2–1
	F	1910	0	MNS	R_1r	+	+	—	+	—	1–1
	F	1935	0	MNS	R_1R_1	+	—	—	+	—	1–1
	M	1937	0	MS	R_1r	+	—	—	+	—	1–1
	F	1938	0	MNs	R_1R_1	—	—	—	+	—	1–1
G 105	M	1895	A_1	Ns	R_1r	+	—	—	+	+	1–1
	F	1898	0	MNS	R_1R_1	+	—	—	+	+	1–1
	M	1924	A_1	Ns	R_1r	+	—	—	+	—	1–1
	F	1927	A_1	Ns	R_1R_1	+	—	—	+	—	1–1
G 106	M	1911	B	Ns	R_2r	+	—	—	—	—	2–1
	F	1915	A_1	MNS	R_1r	+	—	—	+	—	1–1
	M	1938	B	MNS	R_1R_2	+	—	—	+	—	1–1
	M	1941	0	MNS	rr	+	—	—	—	—	1–1
	F	1943	A_1B	MNS	R_2r	+	—	—	+	—	1–1
G 107	M	1908	A_1	Ms	R_1R_1	+	—	—	+	+	2–1
	F	1913	A_1	MNS	R_1r	+	+	—	+	—	1–1
	F ⎱	1941	A_1	MS	R_1r	+	+	—	+	—	1–1
	M ⎰	1941	A_1	MNs	R_1R_1	+	—	—	+	+	2–1
G 108	M	1910	B	MNs	R_1R_1	—	+	+	+	—	2–2
	F	1915	0	Ms	R_2r	+	—	—	+	+	2–2
	M	1941	B	MNs	R_1r	+	+	+	+	+	2–2
	M	1944	B	MNs	R_1R_2	+	+	+	+	+	2–2

No.	Sex	Y. of b.	AB0	MNS	Rh	P	Le(a)	K	Lu(a)	Fy(a)	Gm(a)	Hp
H 1	M	1912	A_1	MNs	R_1R'	—	—	—	—	+	—	2–2
	F	1920	B	MNS	rr	+	—	—	—	+	+	2–1
	M	1940	A_1B	MNs	R_1r	+	—	—		—	+	2–1
	F	1943	A_1	MNS	$R'r$	+	—	—		+	—	u.
H 3	M	1909	0	NS	R_1r	+	+	—	—	+	—	1–1
	F	1911	0	MNs	rr	+	+	—	—	—	—	2–1
	F	1935	0	MNS	R_1r	+	+	—		+	—	2–1
	M	1937	0	MNs	rr	+	+	—		+	—	2–1
	F	1939	0	MNS	R_1r	+	+	—		+	—	2–1
	F	1940	0	Ns	R_1r	+	+	—	—	+	—	2–1
	M	1942	0	MNS	rr	+	+	—		+	—	1–1
H 5	M	1909	0	MNS	R_1r	+	—	—	+	—		2–2
	F	1913	B	MS	R_2r	—	—	—	—	—	—	2–1
	M	1940	0	MNS	rr	+	—	—	—	—		2–1
	F	1944	B	MS	rr	+	—	—	+	—	+	2–1

No.	Sex	Y. of b.	AB0	MNS	Rh	P	Le(a)	K	Lu(a)	Fy(a)	Gm(a)	Hp
H 7	M	1904	0	Ns	R_1R_z	+	+	—	—	—	—	2-2
	F	1904	0	Ns	rr	+	—	—	—	—	—	2-1
	M	1941	0	Ns	R_1r	—	+	—		—	—	2-2
H 8	M	1915	A_2	MNs	R_1r	+	—	—		+		2-2
	F	1912	B	MNS	R_1R_2	+	—	—	—	+	+	2-2
	F	1943	0	MNs	R_1r	+	—	—	—	+	+	2-2
	M	1946	0	Ns	R_1R_1	+	—	—		+		2-2
H 9	M	1908	0	MS	R_1r	+	÷	+	—	—	+	2-1
	F	1907	0	Ms	R_1R_1	+	—	—	—	+	+	2-1
	M	1943	0	MS	R_1r	+	—	+	—	+	+	2-2
	M	1945	0	MS	R_1r	+	—	—	—	—	—	2-1
H 10	M	1914	0	MS	rr	+	+	—	—	—	—	2-2
	F	1909	A_1	MNs	R_1r	+	—	—	—	+	+	2-2
	F	1939	A_1	MS	R_1r	+	—	—		+		2-2
	M	1941	A_1	MNs	rr	+	—	—	—	+	—	2-2
	M	1947	A_1	Ms	R_1r	+	—	—		+	—	2-2
H 12	M	1916	0	Ns	R_1R_2	+	—	—	+	—	—	2-1
	F	1918	A_1	MS	rr	+	—	—	—	—	+	2-2
	M	1941	A_1	MNS	R_2r	+	—	—	+	—	—	2-2
	M	1942	A_1	MNS	R_2r	—	—	—	+	—	+	2-1
	F	1945	A_1	MNs	R_2r	+	—	—	—	—	+	2-2
H 13	M	1908	A_1	MS	rr	—	+	—		—	—	2-2
	F	1914	A_1	MNs	R_1r	+	—	—	—	—	—	2-2
	F	1942	A_1	MNS	R_1r	+	—	—	—	—	—	2-2
	M⎫	1946	A_1	MS	rr	+	—	—		—	—	u.
	F⎬	1946	A_1	MS	R_1r	+	—	—		—	—	u.
H 14	M	1904	0	MNS	R_1r	—	—	—	—	—	—	2-2
	F	1909	0	Ms	R_1R_1	—	—	—	—	—	—	1-1
	M	1943	0	MNs	R_1r	—	—	—	—	—	—	2-1
H 17	M	1900	0	MNs	R_1R_2	+	—	—	—	—	—	2-2
	F	1905	0	MS	R_1r	+	—	—	—	+	+	2-1
	F	1931	0	Ms	R_2r	+	—	—	—	+	+	2-1
	M	1932	0	Ms	R_1R_2	+	—	—		+	—	2-2
	M	1935	0	MS	R_1R_1	+	—	—	—	+	+	2-2
	M	1939	0	MS	R_1R_1	+	—	—	—	—	+	2-1
	M	1944	0	MNs	R_1r	+	÷	—		+	—	2-1
H 18	M	1910	A_1	MS	R_1r	—	—	—	—	—	—	2-1
	F	1915	A_1	MS	R_2r	+	—	—	—	—	+	2-1
	M	1937	A_1	Ms	rr	+	—	—	—	—	+	2-2
	F	1943	A_1	Ms	R_1R_2	+	+	—		—	+	2-1
H 19	M	1908	0	Ms	R_1r	+	—	—	—	+	+	2-2
	F	1913	0	MNs	R_1r	+	—	—		+		2-1
	M	1937	0	MNs	R_1R_1	+	—	—		+	—	2-1
	F	1943	0	MNs	R_1R_1	+	—	—	—	+	+	2-1
H 20	M	1913	0	MS	R_1r	+	—	—	—	+	—	2-1
	F	1917	0	MS	R_1R_1	+	—	—	—	+	—	2-1
	F	1941	0	MS	R_1r	+	—	—	—	+	—	2-1
H 21	M	1904	0	MS	rr	—	—	—	—	+		2-2
	F	1903	0	Ms	$R''r$	+	—	—	—	+		2-1
	F	1938	0	Ms	rr	+	—	—		+		2-1
	F	1942	0	Ms	$R''r$	+	—	—		+		2-2

No.	Sex	Y. of b.	AB0	MNS	Rh	P	Le(a)	K	Lu(a)	Fy(a)	Gm(a)	Hp
H 22	M	1914	0	MNS	R_1r	+	—	+	—	+		2–2
	F	1919	0	MNS	rr	+	+	—	—	—	—	2–1
	M	1940	0	MNS	rr	+	—	—		+	+	2–2
	M	1945	0	MS	rr	+	—	—		—	+	2–2
	M	1947	0	Ns	rr	+	+	—		+	+	2–1
H 23	M	1906	A_1	MS	R_1R_1	+	+	—		+		2–2
	F	1910	0	Ms	R_2r	+	—	—		+		2–2
	M	1940	A_1	MS	R_1r	+	+	—		+		2–2
H 24	M	1918	0	MNs	R_0R_2	—	—	—	—	+	+	2–1
	F	1912	B	Ns	rr	—	—	—	—	+	+	1–1
	F	1943	0	Ns	R_0r	—	—	—		+	+	1–1
H 26	M	1907	A_1	MNs	rr	—	—	—	—	+	+	2–1
	F	1912	A_1	MNs	R_1R_1	—	—	—	—	+	—	2–1
	M	1936	A_1	Ns	R_1r	—	—	—	—	+	—	2–1
	F	1943	A_1	MNs	R_1r	—	—	—	—	—	+	1–1
H 27	M	1902	0	MNs	R_1R_1	+	—	—	—	+	—	1–1
	F	1901	A_1	MNS	R_1R_2	—	—	—	—	+	—	2–1
	F	1932	0	MNs	R_1R_2	+	—	—	—	—	—	1–1
	F	1941	0	MS	R_1R_2	+	—	—		+	—	2–1
H 28	M	1919	0	Ns	R_1R_2	—	—	—	—	+	—	2–2
	F	1917	B	NS	R_2r	+	—	—	+	+	+	2–2
	F	1942	0	NS	R_1r	+	—	—	+	+	+	2–2
	F	1944	B	NS	R_2r	—	—	—	—	+	+	2–2
H 29	M	1908	0	MNS	R_1R_2	—	+	—	—	+		2–1
	F	1917	0	NS	R_2r	+	+	—	—	+		2–2
	F	1938	0	NS	R_2r	+	+	—		+		2–1
	M	1939	0	MNS	R_1r	—	+	—	—	+	—	2–2
	F	1944	0	MNs	R_2r	—	+	—		+		2–1
H 30	M	1917	0	NS	R_1R_1	+	—	—	—	+	—	2–1
	F	1918	A_1	MS	R_1R_2	+	—	—	—	—	+	2–1
	M	1940	0	MNS	R_1R_2	+	—	—	—	—	—	2–2
	M	1941	0	MNs	R_1R_1	+	—	—	—	—		2–2
	F	1944	0	MNS	R_1R_1	+	—	—	—	+	+	2–1
H 31	M	1912	0	MNs	R_1r	+	+	—	—	—	—	2–1
	F	1920	A_2B	MNS	rr	+	—	—	—	—	+	2–1
	M	1943	A_2	MNs	rr	+	—	—		—	+	2–1
H 34	M	1911	A_1B	MNs	R_2R_2	+	—	—	—	+	+	1–1
	F	1913	0	Ms	R_2r	+	—	—	—	+	+	2–1
	M	1940	A_1	MNs	R_2r	+	—	—		+	+	2–1
	F	1942	A_1	Ms	R_2r	+	—	—		+		2–1
	F	1945	A_1	Ms	R_2r	+	—	—		+	+	2–1
	F	1947	B	Ms	R_2R_2	+	—			+	+	2–1
H 35	M	1902	A_1	MNs	R_1R_2	—	+	—	—	+	—	2–1
	F	1905	A_1	MNS	R_1r	—	—	—	—	—	+	2–1
	F	1944	A_1	MS	R_2r	—	—	—		+	—	2–2
H 38	M	1916	0	MS	R_1R_1	—	—	—	—	+	—	2–1
	F	1919	0	MS	rr	+	—	—	—	+	—	1–1
	M	1944	0	MS	R_1r	+	—	—	—	+	—	2–1
	F	1949	0	MS	R_1r	—	—	—	—	+	—	2–1

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No.	Sex	Y. of b.	AB0	MNS	Rh	P	Le(a)	K	Lu(a)	Fy(a)	Gm(a)	Hp
H 39	M	1908	A_1	Ms	R_1r	—	+	—	+	—	+	2–1
	F	1910	B	MNS	$R'r$	+	+	+	—	+	+	2–1
	F	1932	B	MS	rr	+	+	—	+	—	+	1–1
	F	1938	B	MS	rr	+	+	+	+	—	—	1–1
	M	1940	A_1	MNS	R_1r	—	+	+	+	—	+	2–1
	M	1943	A_1	MS	R_1R'	+	+	—	—	+		2–1
H 40	M	1910	A_2	NS	R_1r	+	—	—	—	+	+	2–2
	F	1912	B	MNS	R_1R_1	—	—	—	—	.	—	2–2
	F	1936	B	MNS	R_1r	+	—	—	—	—	—	2–2
	F	1941	A_2B	NS	R_1r	-	+	—		—	—	2–2
	F	1942	A_2B	MNS	R_1R_1	—	+	—		—	+	2–2
H 41	M	1904	A_1	MNS	R_2r	—	—	—	—	.	+	2–2
	F	1905	0	Ms	R_1R_1	—	—	—	—	—	—	1–1
	M	1935	0	MNs	R_1r	—	—	—		.	+	2–1
	F	1936	0	MNs	R_1R_2	—	—	—		—	+	2–1
	F	1937	A_1	MS	R_1R_2	—	—	—		—	+	2–1
	M	1939	A_1	MNs	R_1r	—	—	—		—	+	2–1
	F	1944	0	MS	R_1r	—	—	—		.	+	2–1
H 42	M	1902	0	MNs	R_1r	-	—	—	—	—	+	2–1
	F	1909	A_1	Ms	R_1r	-	—	—	—	.	+	2–1
	F	1938	0	MNs	R_1r	—	—	—	—	—	+	2–1
	M	1940	A_1	MNs	R_1r	—	—	—	—	+	+	2–2
	F	1940	A_1	Ms	R_1r	-	—	—		+	+	2–1
H 44	M	1905	A_1	MS	R_1R_1	-	—	—		+	—	2–1
	F	1913	A_1	Ns	R_1R_1	—	—	—	—	+	—	2–1
	M	1939	A_2	MNS	R_1R_1	—	—	—		+	—	2–2
	M	1940	A_1	MNS	R_1R_1	—	—	—		+	—	2–1
	F	1943	A_1	MNS	R_1R_1	-	—	—		+	—	2–1
	M	1947	A_1	MNS	R_1R_1	—	—	—		+	—	1–1
H 45	M	1921	0	Ns	R_1r	-	—	—	—	—	—	2–2
	F	1924	A_1	MNs	R_2r	-	—	—	—	+	+	2–1
	M	1946	0	MNs	rr	—	—	—	—	+	+	2–1
H 46	M	1897	A_1	Ns	R_1R_1	+	—	—	—	+	+	2–1
	F	1904	A_1	MNs	R_1R_2	-	—	—	—	—	+	2–2
	F	1924	A_1	MNs	R_1R_1	+	—	—		—		
	F⟩	1932	A_1	MNs	R_1R_1	+	—	—		-		2–1
	F⟨	1932	A_1	Ns	R_1R_1	+	—	—		+		2–2
	F	1941	0	Ns	R_1R_1	+	—	—		+	+	2–1
H 47	M	1915	0	MNs	R_1r	+	—	—	—	+	+	2–1
	F	1919	A_1	MS	R_1R_1	+	—	—	—	+	+	2–1
	M	1942	A_1	MS	R_1r	+	—	—	—	—	+	2–1
H 49	M	1898	0	MS	R_1R_1	+	+	—	—	+	+	2–1
	F	1907	A_1	MNs	R_1R_2	+	—	—	—	—	—	2–1
	F	1938	0	MNS	R_1R_1	+	+	—		—	—	2–1
	F	1941	A_1	MNs	R_1R_2	+	+	—	—	+	—	2–2
H 50	M	1916	0	MNs	rr	—	—	—	—	+	—	2–2
	F	1924	0	MNs	R_1r	+	—	—	—	—	+	2–1
	F	1945	0	MNs	rr	—	—	—	—	—	+	2–2
H 52	M	1912	0	MNs	R_1r	—	—	—		+	—	2–2
	F	1912	A_2	MNS	R_1r	+	—	—		+	—	1–1
	M	1940	0	MS	R_1r	—	—	—	—	+	—	2–1

No.	Sex	Y.of b.	AB0	MNS	Rh	P	Le(a)	K	Lu(a)	Fy(a)	Gm(a)	Hp
H 53	M	1922	0	MS	R_1R''	+	+	—	—	+	+	2–1
	F	1917	A_1	NS	rr	+	—	—	—	+	+	1–1
	M	1943	A_1	MNS	$R''r$	+	—	—		+	+	1–1
	F	1945	A_1	MNS	$R''r$	—	—	—		+	+	1–1
H 54	M	1915	0	Ms	R_1r	+	—	—	—	+	+	2–2
	F	1922	0	MS	R_1r	—	—	—	—	—	—	2–1
	M	1942	0	MS	R_1r	+	—	—		+	—	2–2
	M	1945	0	MS	R_1R_1	—	—	—		—	—	2–1
H 55	M	1911	0	MNS	R_1R_1	+	—	—	—	—	+	2–2
	F	1914	0	MNS	R_1r	+	+	—	—	—		2–1
	F	1939	0	MNS	R_1R_1	+	—	—	—	—	+	2–1
	F	1942	0	MNS	R_1r	+	+	—	—	—	+	2–1
	F	1944	0	MNS	R_1R_1	+	+	—	—	—	—	2–2
	F	1946	0	Ns	R_1R_1	+	—	—	—	—	+	2–1
H 56	M	1915	0	MNS	R_1r	+	+	—	—	+	+	2–1
	F	1915	A_2	MNs	R_1R_2	—	—	—	—	+	+	2–1
	M	1941	0	Ns	R_1r	—	+	—		+	+	2–2
	F	1943	A_2	MNs	R_2r	—	—	—		+	+	2–2
	M	1947	A_2	MNs	R_1R_2	+	—	—		+	—	1–1
H 57	M	1911	0	MNs	R_1r	+	—	—	—	—	+	2–2
	F	1911	A_1	MNs	R_1r	+	—	—	—	—	—	2–1
	F	1938	0	Ms	R_1r	+	—	—		—	+	2–1
	F	1942	0	Ms	R_1R_1	+	—	—		—	—	2–1
	M	1947	A_1	Ns	R_1r	+	—	—		—	—	2–1
H 58	M	1918	0	MNS	R_1r	+	—	—	—	—	+	2–2
	F	1925	0	MS	rr	+	—	—	—	+	—	2–2
	M	1947	0	MNs	rr	+	—	—	—	—	—	u.
H 60	M	1918	0	MNs	R_1R_1	—	—	—	+	+	—	2–2
	F	1918	A_1	Ns	R_1R_1	+	—	—	—	+	+	2–1
	F	1941	0	MNs	R_1R_1	—	—	—	+	+	—	2–1
	F	1943	0	Ns	R_1R_1	—	—	—	+	+	—	2–2
	M	1945	0	Ns	R_1R_1	+	—	—	—	+	+	2–1
H 61	M	1914	A_1	MS	R_2r	+	—	—	—	+	+	1–1
	F	1919	A_1	Ms	R_1r	+	+	—	—	+	—	2–2
	M	1940	A_1	MS	R_2r	+	—	—		—	+	2–1
	F	1946	A_1	MS	R_1r	+	—	—		+	+	2–1
H 62	M	1923	0	MNs	R_1R_1	+	—	—		—		2–1
	F	1921	0	MNs	R_2r	+	—	—		+		2–1
	F	1944	0	Ms	R_1R_2	+	—	—	—	—	+	2–1
	M	1947	0	Ms	R_1R_2	+	—	—	—	—	—	2–1
H 64	M	1918	A_2	MNS	rr	+	—	—	—	+	+	2–2
	F	1918	A_1	MNS	R_2r	—	—	—	—	+	+	2–1
	F	1947	A_1	MNS	rr	—	—	—	—	+	+	2–2
H 65	M	1914	0	MNS	rr	+	—	—	—	+		2–1
	F	1919	A_1	Ms	R_1R_1	+	—	+	—	—		1–1
	F⎱	1939	A_1	MNs	R_1r	+	—	—		—		2–1
	F⎰	1939	A_1	MS	R_1r	—	—	—		—		2–1
H 66	M	1906	A_1	MS	R_2r	—	+	—	—	+	+	2–2
	F	1907	A_1	Ms	R_1R_2	+	—	—	—	—	+	2–1
	M	1935	A_1	Ms	R_1r	+	—	—		—	+	2–1
	M	1936	A_1	MS	R_2r	—	—	—		+		2–1
	M⎱	1940	A_2	MS	R_1R_2	—	—	—		+		2–2
	F⎰	1940	A_1	Ms	R_2r	—	+	—		—	+	2–1

No.	Sex	Y. of b.	ABO	MNS	Rh	P	Le(a)	K	Lu(a)	Fy(a)	Gm(a)	Hp
H 67	M	1921	0	MNs	R_1R_2	+	−	−	−	+	+	2–1
	F	1921	0	MNS	R_2r	+	+	−	−	+	−	2–1
	M	1944	0	Ns	R_2R_2	+	−	−		+	+	2–1
	M	1945	0	MNS	R_1r	+	−	−		+	−	1–1
	M	1947	0	MNs	R_1r	+	−	−		+	−	1–1
H 68	M	1911	0	Ns	R_1r	+	+	−	−	+	+	2–1
	F	1903	A_2B	Ns	R_1R_1	−	−	+	−	+	−	1–1
	M	1947	B	Ns	R_1R_1	−	−	−	−	+	+	2–1
H 69	M	1897	A_1	MNs	R_1R_1	−	−	−		+		2–1
	F	1908	0	MS	R_2r	−	−	−		+		2–1
	F	1944	0	MNs	R_1r	−	−	−		+	+	2–1
H 70	M	1914	A_1	MS	R_1r	+	−	−	−	+	+	2–2
	F	1921	0	MNS	rr	+	−	−	−	+	+	2–2
	F	1942	A_1	MS	R_1r	+	−	−		+	+	2–2
	F	1945	A_1	MNs	R_1r	+	−	−		+	+	2–2
H 72	M	1914	0	MS	rr	−	−	−	−	+	−	2–2
	F	1914	0	MNS	$R'r$	+	−	−		−	−	2–2
	M	1939	0	MNS	rr	+	−	−		+	−	2–2
	M	1943	0	MS	$R'r$	−	−	−		+	−	2–2
	F	1944	0	MS	rr	+	−	−		+	−	2–2
H 73	M	1909	A_1	MNS	R_1R_1	−	−	−	−	+	+	2–1
	F	1919	B	MNS	R_1R_1	+	−	−	−	+	+	1–1
	M	1940	0	Ms	R_1R_1	−	−	−	−	+	+	1–1
	F	1942	B	MNS	R_1R_1	+	−	−		+	+	1–1
	F	1943	A_1	MNS	R_1R_1	−	−	−	−	+		2–1
	M	1944	0	Ms	R_1R_1	−	−	−	−	−	+	1–1
	M	1945	0	MNS	R_1R_1	−	−	−		+	+	1–1
	M	1947	A_1B	Ms	R_1R_1	+	−	−		+		2–1
H 74	M	1914	A_1	MNs	R_1R_2	+	+	−	−	−	−	2–1
	F	1921	B	MNs	R_1r	+	−	−	+	−	+	2–2
	F	1943	A_1B	MNs	R_1r	+	+	−	−	−	−	2–2
H 76	M	1902	0	Ns	R_1r	+	+	−	−	+	+	2–2
	F	1912	A_1	MS	rr	+	−	−	−	+	−	2–1
	M	1934	A_1	MNS	R_1r	−	−	−		+	+	2–1
	F	1935	A_1	MNS	rr	+	−	−		+	+	2–1
	M	1941	0	MNs	rr	+	−	−		+	+	2–2
	M	1947	A_1	MNs	R_1r	−	−	−		.	−	2–1
H 77	M	1902	0	Ms	R_1r	+	−	−	−	+	+	2–2
	F	1909	B	NS	R_1r	+	−	−	−	−	−	2–2
	M	1931	B	MNs	R_1r	+	−	−	−	−		2–2
	M	1942	0	MNs	rr	−	−	−	−	−		2–2
H 79	M	1886	B	MNs	R_1R_1	−	+	−	−	−	+	1–1
	F	1911	0	MNs	rr	−	−	−	−	−	−	2–1
	F	1943	B	Ns	R_1r	−	−	−		−	+	2–1
	M }	1944	B	MNs	R_1r	−	−	−		−	+	2–1
	F }	1944	0	MNs	R_1r	−	−	−		−	+	1–1
	M	1946	0	MNs	R_1r	−	−	−		−	+	1–1
H 80	M	1901	A_1	MNS	R_2r	−	−	−	+	−	+	2–1
	F	1915	A_2	Ms	R_1r	−	−	−	−	+	+	2–1
	M	1939	0	Ms	R_1r	−	−	−	−	+	−	1–1
H 81	M	1917	0	MNs	R_1R_1	+	−	−		+	+	2–1
	F	1919	0	MNS	R_1r	+	−	−	−	−	+	1–1
	M	1941	0	Ns	R_1R_1	+	−	−	−	+	+	2–1
	F	1942	0	MNS	R_1R_1	+	−	−		+	+	1–1

No.	Sex	Y. of b.	ABO	MNS	Rh	P	Le(a)	K	Lu(a)	Fy(a)	Gm(a)	Hp
H 82	M	1911	0	NS	rr	—	—	—	—	+	—	1–1
	F	1913	0	MS	rr	+	—	—	—	+	+	2–2
	M	1940	0	MNS	rr	+	+	—		+	+	2–1
H 83	M	1894	0	Ns	R_1R_1	+	—	+	—	+	+	2–1
	F	1904	B	MNs	R_1R_2	+	+	—	—	+	+	1–1
	M	1927	B	MNs	R_1R_1	+	—	+		+	+	1–1
	F	1928	0	Ns	R_1R_2	+	—	+		+	+	2–1
	M	1935	B	MNs	R_1R_1	+	—	+		+	+	2–1
	M	1940	0	Ns	R_1R_2	+	—	+	—	+	—	1–1
H 84	M	1912	0	MNS	R_1r	+	+	+	—	+	+	2–1
	F	1910	A_1	NS	R_1R_2	+	—	—	—	+	—	2–1
	M	1936	0	Ns	R_2r	+	—	+		+	—	2–2
	F	1942	0	MNS	R_1r	+	—	—		+	—	1–1
H 85	M	1909	0	Ms	R_1r	—	—	—	+	+	+	2–2
	F	1907	A_1	NS	R_1R_1	+	—	—	—	+	+	2–1
	M	1934	A_1	MNs	R_1r	+	—	—	—	+		2–2
	F	1937	A_1	MNS	R_1r	—	—	—	—	+		2–2
	F	1939	A_1	MNs	R_1r	—	—	—	+	—	+	2–1
	F	1941	0	MNS	R_1R_1	+	—	—	+	+	+	2–1
	M	1942	0	MNS	R_1r	—	—	—	—	+	+	2–1
	M	1945	A_1	MNs	R_1r	+	—	—	—	+	+	2–1
H 88	M	1922	0	MNS	R_1r	—	—	+	—	+	+	2–1
	F	1925	0	Ns	R_1R_1	+	—	—	—	—	+	2–1
	F	1945	0	Ns	R_1R_1	+	—	—	—	+	+	2–1
	F	1946	0	Ns	R_1r	+	—	—		—	—	2–2
H 89	M	1910	A_1	MNS	R_1R_2	+	—	—	—	+	—	1–1
	F	1910	0	Ns	R_1R_2	+	—	—	—	—	—	2–1
	M	1942	A_1	Ns	R_2R_2	+	—	—		—	—	2–1
	M	1944	A_1	Ns	R_1R_2	+	—	—		—		2–1
	F	1946	A_1	MNS	R_1R_2	+	—	—		—	—	2–1
H 90	M	1905	0	Ns	R_2r	+	—	—	—	+	—	2–1
	F	1907	A_1	MNS	R_1r	+	+	—	—	+	+	2–1
	F	1930	A_1	MNS	R_1r	+	+	—	—	—	+	2–1
	F	1942	A_1	Ns	R_1R_2	+	—	—	—	+	—	2–2
H 91	M	1912	0	MNS	R_1r	—	—	—	—	—		2–1
	F	1919	0	MNs	rr	+	—	—	—	—	+	1–1
	M	1944	0	MNS	rr	+	—	—	—	—	+	2–1
	M	1947	0	MS	R_1r	—	—	—	—	—	+	2–1
H 92	M	1912	A_1	Ns	R_1r	+	—	—	+	+	+	2–1
	F	1918	0	Ns	R_2r	+	—	—	—	—	—	1–1
	F	1940	A_1	Ns	R_1r	+	—	—	+	+		2–1
	M	1941	A_1	Ns	R_1r	+	—	—	+	—	+	2–1
H 93	M	1917	A_2B	MS	R_1R_2	—	—	—	—	—	—	2–2
	F	1921	A_1	MS	R_2r	+	—	—	—	+	—	2–1
	M	1942	A_1	MS	R_1R_2	+	—	—		+	—	2–2
	M	1945	A_1B	Ms	R_2r	+	—	—		+	—	2–1
H 94	M	1913	B	Ns	R_1R_2	—	—	—	—	+	+	1–1
	F	1911	A_1	MNS	R_2r	+	—	—	—	+		1–1
	F	1944	A_1	Ns	R_1r	—	—	—	—	+	+	1–1
H 95	M	1916	A_1	MS	R_1r	+	—	—	—	—	—	2–1
	F	1922	A_2	MS	rr	+	—	—	—	—	+	2–2
	F	1943	A_1	MS	rr	+	—	—	—	—	+	2–2
	M	1945	A_1	Ms	R_1r	+	—	—		—	+	2–2

No.	Sex	Y. of b.	AB0	MNS	Rh	P	Le(a)	K	Lu(a)	Fy(a)	Gm(a)	Hp
H 96	M	1909	A_1	MS	R_1r	+	—	+	—	+	+	2–2
	F	1911	0	NS	R_1R_1	+	—	—	—	—	+	2–2
	F	1938	A_1	MNS	R_1r	+	—	—	—	+	+	2–2
	F	1944	0	MNS	R_1R_1	+	—	+	—	+	+	2–2
H 98	M	1919	0	MNS	R_1r	+	+	—	—	+	+	1–1
	F	1923	A_1	MNS	R_1r	+	—	+	—	—	+	2–1
	F	1944	A_1	Ns	R_1r	—	—	+	—	+	+	2–1
H 100	M	1906	0	NS	R_1r	—	+	—	—	—	—	2–1
	F	1910	0	MNS	R_1R''	+	+	—	+	+	—	2–1
	F	1938	0	Ns	$R''r$	+	+	—	—	—	—	1–1
	F	1941	0	Ns	R_1r	+	+	—	—	—		2–1
H 101	M	1915	0	MNS	R_1r	+	—	—		+	+	2–1
	F	1914	0	MNS	R_1r	+	—	—	—	+	—	2–1
	F	1944	0	MNS	rr	—	—	—	—	+	+	1–1
H 103	M	1917	0	MNs	R_1R_1	—	—	—	—	+	+	2–1
	F	1918	A_1	MNs	R_1R_1	+	—	—	—	+	—	2–1
	F	1940	A_1	MNs	R_1R_1	—	—	—	—	—	+	2–1
	F	1942	A_1	MNs	R_1R_1	+	—	—	—	—	+	2–1
	F	1944	0	MNs	R_1R_1	+	—	—	—	—	—	2–1
H 104	M	1911	A_1	MS	R_1r	+	+	—	—	+	+	2–1
	F	1914	A_1	NS	R_1R_2	+	—	—	—	+	+	2–1
	F	1945	A_1	MNS	R_1R_2	+	—	—	—	+	—	2–1
H 105	M	1907	0	MS	R_1R_2	+	+	—	—	—	+	2–1
	F	1915	A_1	Ns	R_1R_2	+	—	—	—	—	+	2–2
	F	1939	0	MNS	R_1R_2	+	—	—	.	—	+	2–1
	F	1943	A_1	MNS	R_1R_2	+	—	—	—	—	+	2–1
H 106	M	1917	A_2B	MNS	R_2r	+	—	—	—	—	—	2–2
	F	1918	0	MS	R_1r	+	—	—	—	+	+	2–1
	M	1943	A_2	MS	rr	+	—	—	—	+	+	2–1
	M	1946	A_2	MNS	R_1R_2	+	—	—	—	+	+	2–1
H 107	M	1927	0	Ms	R_1r	+	—	—		+	—	2–1
	F	1928	A_2	MS	R_1r	+	—	—	—	+	—	2–1
	M	1948	0	MS	R_1R_1	+	—	—	—	+	—	2–1
H 109	M	1914	0	MNs	rr	+	—	—	+	—	+	2–1
	F	1913	A_1	MNS	R_1r	—	—	—	—	—	+	2–1
	M	1940	0	MS	rr	+	—	—	—	—	+	2–1
	M	1945	0	Ns	rr	+	—	—	—	—	+	2–1
H 110	M	1908	A_1	MNs	rr	—	—	+	+	+	—	2–2
	F	1913	0	Ms	R_0r	+	—	+	—	+	—	2–2
	M	1932	A_1	Ms	rr	+	—	+	—	+	—	2–2
	F	1934	0	MNs	R_0r	+	—	—	—	+	—	2–2
	M	1936	A_1	Ms	R_0r	+	—	+	+	+	—	2–2
	M	1940	0	MNs	R_0r	+	—	+	—	+	—	2–2
	F	1942	0	Ms	rr	+	—	—	+	+	—	2–2
	M	1945	0	MNs	rr	+	—	+	—	+	—	2–2
H 111	M	1902	B	MNS	rr	+	—	+	—	+	—	2–2
	F	1905	A_1	Ns	R_2r	+	—	—	—	+	—	2–2
	F	1937	A_1	MNS	R_2r	—	—	+		+	—	2–2
	M	1940	0	NS	R_2r	—	—	—		+	—	2–2
H 112	M	1902	0	Ns	rr	+	—	—		—	—	2–1
	F	1917	A_1	MNs	R_1r	—	—	—		+	+	2–2
	F⎱	1942	0	Ns	rr	—	—	—	—	—	—	2–2
	F⎰	1942	0	Ns	rr	—	—	—	—	—	—	2–2

DIAGNOSTIC DERMATOGLYPHIQUE DE LA
BRACHY-MESOPHALANGIE

Par J. LEJEUNE (Paris), E. MARGOLIS (Jerusalem)
et R. TURPIN (Paris)

L'un de nous (1) a récemment publié un cas de Brachy-mésophalangie transmise selon le mode dominant dans une famille présentant par ailleurs des cas de Brachy-téléphalangie.

Une nouvelle observation familiale de Brachy-mésophalangie nous a conduit à étudier les structures épidermiques palmaires des sujets atteints de cette affection et la concordance des anomalies dermatoglyphiques observées dans ces deux familles semble justifier la présente communication.
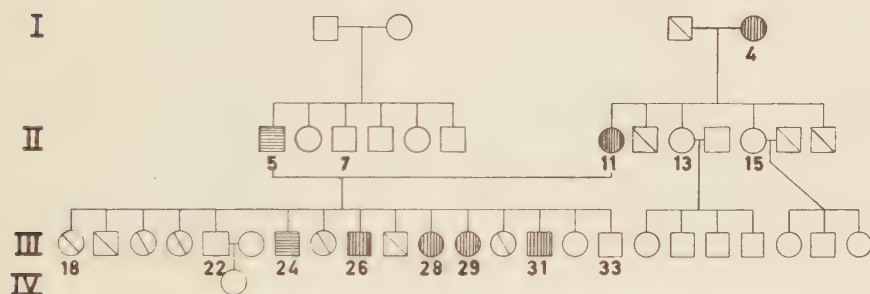
Fig. 1 – Deux anomalies dans la même famille – Les lignes horizontales à l'intérieur des figures indiquent une Brachytéléphalangie transmise par le père. Les lignes verticales indiquent une Brachymésophalangie transmise par la mère. Les lignes diagonales indiquent que les sujets sont décédés ou n'ont pas été testés. (1)

L'anomalie est caractérisée par un raccourcissement de certains doigts (le II et le V) et l'examen radiologique révèle que la lésion siège au niveau de la 2e phalange dont le développement longitudinal est incomplet, alors que les autres segments osseux sont apparemment normaux.

Description des sujets examinés

Famille I

Sujet I, 4

Lésion observée: l'index et l'auriculaire des deux mains sont atteints, par raccourcissement de la 2e phalange, la 1re et la seconde étant normales.

Du point de vue dermatoglyphique (*) on note:

		Main droite	Main gauche
Paume	{	a_4 b_5 c_5 d_7 Boucle radiale	a_4 b_5 c_5 d_7 Boucle radiale
Doigts	{	Les 2 plis de flexion de l'index et du Ve sont très nettement rapprochés l'un de l'autre. Aux autres doigts, les plis de flexion sont normalement écartés.	Les 2 plis de flexion de l'index et du Ve sont très nettement rapprochés l'un de l'autre.

Sujet II, 11

Lésions observées: identiques à I,4.

Dermatoglyphes:

		Main droite	Main gauche
Paume	{	a_4 b_5 c_5 d_7 Pas de boucle hypothénarienne	a_4 b_5 c_5 d_7 Boucle radiale
Doigts	{	Rapprochement des 2 plis de flexion à l'index et au Ve (extrêmement marqué à l'index) Aux autres doigts les plis de flexion sont normalement écartés.	Rapprochement des 2 plis de flexion à l'index et au Ve (extrêmement marqué à l'index)

Sujet III, 26

Lésion observées: Brachy-mésophalangie des II, III et V aux deux mains. De plus à droite et à gauche le premier métacarpien est court et trapu.

Dermatoglyphes:

		Main droite	Main gauche
Paume	{	a_5 b_7 c_9 d_{11} Pas de boucle hypothénarienne	a_5 b_7 c_9 d_{11} Boucle radiale

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(*) Pour la terminologie employée, conforme à la nomenclature habituelle, cf. *R. Turpin* et *J. Lejeune*, 1955 (2).

Doigts	Rapprochement des 2 plis de flexion, marqué au IIIe, très marqué au Ve	Rapprochement des 2 plis de flexion, marqué au IIIe, très marqué au Ve
	Un seul pli de flexion à l'index	*Un seul pli de flexion à l'index*

Sujet III, 28

Lésions observées, Brachy-mésophalangie importante des II, III et V aux deux mains. Dermatoglyphes:

	Main droite	Main gauche
Paume	a_5 b_7 c_9 d_{11} Boucle radiale	a_5 b_7 c_9 d_{11} Boucle radiale
Doigts	Rapprochement des 2 plis de flexion au Ve *Un seul pli de flexion au IIIe et au IIe.*	Rapprochement des 2 plis de flexion au Ve *Un seul pli de flexion au IIIe et au IIe.*

Sujet III, 29

Lésions observées: Brachy-mésophalangie du IIe et V^e aux deux mains. Dermatoglyphes:

	Main droite	Main gauche
Paume	a_4 b_5 c_7 d_9 Pas de boucles hypothénariennes	a_4 b_5 c_x d_9 Pas de boucles hypothénariennes
Doigts	Les 2 plis de flexions sont rapprochés nettement au Ve et au IIe, légèrement au IIIe	Les 2 plis de flexion sont rapprochés nettement au Ve, un peu au IIe et sont normalement écartés au IIIe

Sujet III, 31

Lésions observées: Brachy-mésophalangie marquée des IIe, IIIe, IVe et V^e, aux deux mains.
Dermatoglyphes:

	Main droite	Main gauche
Paume	a_5 b_7 c_9 d_{11} Boucle radiale *Pli palmaire transverse*	a_5 b_7 c_9 d_{11} Boucle radiale *Pli palmaire transverse*

Doigts	Rapprochement des 2 plis de flexion au IVe Rapprochement des 2 plis de flexion au IVe

Rapprochement des 2 plis
de flexion au IVe

Rapprochement des 2 plis
de flexion au IVe

*Un seul pli de flexion aux
IIe, IIIe et V^e.*

*Un seul pli de flexion aux
IIe, IIIe et V^e.*
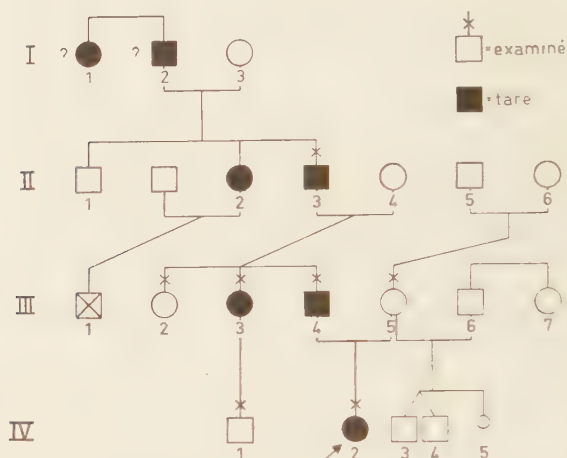
Fig. 2. Famille II (Fam. V. M., Paris)

Famille II

Sujet II, 3

Brachy-mésophalangie intense des IIe, IIIe, IVe, et V^e, la radiologie révélant une aplasie intense de la 2e phalange (quasi inexistante au IIe), les autres étant apparemment normales.

Dermatoglyphes: (fig. 3)

	Main droite	Main gauche
Paume	a_5 b_7 c_x d_{11} *Pli palmaire transverse*	a_5 b_7 c_x d_{11} *Pli palmaire transverse*
Doigts	Rapprochement des 2 plis de flexion du IVe *Pli de flexion unique IIe, IIIe et V^e*	Rapprochement des 2 plis de flexion du IVe *Pli de flexion unique IIe, IIIe et V^e*

Fig. 3. Sujet II, 3 de la famille II

Sujet III, 3

Brachy-mésophalangie modérée du IIe et du Ve aux deux mains.
Dermatoglyphes:

		Main droite	Main gauche
Paume	{	a_5 b_8 c_{10} d_{11} t'' boucle cubitale	a_5 b_7 c_9 d_{11} t' boucle cubitale
Doigts	{	Rapprochement des 2 plis de flexion au IIe et au Ve	Rapprochement des 2 plis de flexion au IIe et au Ve

Sujet III, 4

Brachy-mésophalangie modérée du IIe et du Ve aux deux mains.
Dermatoglyphes:

		Main droite	Main gauche
Paume	{	a_4 b_7 c_9 d_{11} Boucle radiale	a_4 b_7 c_x d_{11} Boucle radiale
Doigts	{	Rapprochement des 2 plis de flexion du IIe et V^e	Rapprochement des 2 plis de flexion du IIe et V^e

Sujet IV, 2

Mongolienne, proposante à partir de laquelle ont été observées les anomalies familiales. Brachy-mésophalangie intense du IIe et du Ve, modérée au IIIe et IVe.

Dermatoglyphes:

		Main droite	Main gauche
Paume	{	a_5 b_7 c_9 d_{11} t″ boucle cubitale (*)	a_5 b_7 c_9 d_{11} t″ boucle cubitale (*)
Doigts	{	Rapprochement des 2 plis de flexion des IIIe et IVe	Rapprochement des 2 plis de flexion du IIIe et du IVe
		Pli de flexion unique au IIe et au Ve	*Pli de flexion unique au IIe et au Ve*

*) Disposition typique du mongolisme.

Conclusion et Résumé

Le parallélisme strict entre les lésions observées dans ces deux familles, tant au point de vue clinique et radiologique, qu'au point de vue dermatoglyphique et génétique permet semble-t-il d'individualiser la Brachymésophalangie en tant qu'entité distincte, d'hérédité strictement dominante.

Il existe une certaine variabilité dans la gravité de l'atteinte, mais le parallélisme entre les lésions cliniques et radiologiques d'une part et les troubles dermatoglyphiques d'autre part est extrêmement frappant.

On peut brièvement résumer les constatations précédentes en disant qu'à un degré modéré de brachy-mésophalangie correspond un rapprochement des 2 plis de flexion des doigts atteints, rapprochement qui coïncide avec l'hypodéveloppement de la 2e phalange, décelable radiologiquement.

A un degré plus grave, lorsque la seconde phalange est très aplasique on observe plus qu'un seul pli de flexion au niveau des doigts atteints.

Enfin lorsque tous les doigts sont atteints (en général seuls le IIe et le Ve le sont) on observe une transversalité marquée des crêtes papillaires de la partie distale de la paume, et une coalescence des plis de flexion de la paume, réalisant le classique pli palmaire transverse.

Le fait que cette anomalie ait été retrouvé chez une mongolienne et ses ascendants pose par ailleurs le problème d'une relation éventuelle entre le Brachy-mésophalangie et la dystrophie mongoloïde.

Summary

Two families with multiple occurence of brachymesophalangy are described. The clinical, radiological, dermatoglyphical and genetical findings in these two families are so similar that the presence of a genetic entity is suggested. It seems to be transmitted as a Mendelian dominant with some variation in degree of manifestation.

The clinical and radiological picture is found to be closely correlated with the abnormalities seen in the dermal ridge-pattern on the fingers and palm. The pathological changes are primarily seen in the second and fifth finger. Here the middle phalanx shows varying degree of hypoplasia in the longitudinal direction as demonstrated by X-rays, followed by a decrease in the distance between the two flexion creases on the fingers affected; in severe cases these two lines may fuse completely. In case all fingers are affected the dermal ridges on the distal part of the palm show a characteristic transversality and a fusion of the transverse palmar flexion creases resulting in a single, transversal palmar line.

As this anomaly has been seen in a mongol and some of her relatives a connection may exist between brachymesophalangy and mongoloid dystrophy.

Zusammenfassung

Diese beiden Familien verhalten sich in den beobachteten Anomalien sowohl in bezug auf das klinische und radiologische Bild als auch in den Tastleisten und in ihrer Genetik genau gleich. Deshalb ist es gestattet, die Brachymesophalangie als einen besonderen, streng dominant erblichen Biotyp zu betrachten.

In der Expressivität beobachtet man eine gewisse Variabilität, aber der Parallelismus zwischen den klinischen und radiologischen Veränderungen einerseits und den Abweichungen der Tastleisten auf der anderen Seite tritt überaus deutlich hervor.

Man kann die oben dargestellten Schlußfolgerungen folgendermaßen kurz zusammenfassen: Einem geringen Ausmaß der Brachymesophalangie entspricht ein Zusammenrücken der beiden Flexionsfalten der befallenen Finger, das mit einer radiologisch nachweisbaren Unterentwicklung der 2. Phalanx verbunden ist.

Bei einem schweren Grad der Störung, wenn die 2. Phalanx aplastisch ist, sieht man nur eine Flexionsfalte an den befallenen Fingern.

In der Regel sind nur der 2. und der 5. Finger betroffen. Wenn aber alle Finger das Merkmal aufweisen, beobachtet man, daß die Papillarleisten in der distalen Partie der Palma deutlich in Querrichtung verlaufen, während die Flexionsfalten der Palma zusammengewachsen sind und so die klassische quere Palmarfalte ergeben.

Die Tatsache, daß diese Anomalie bei einem Mädchen mit mongoloider Idiotie und bei ihren Vorfahren gefunden wurde, wirft von einer anderen Seite her das Problem auf, ob vielleicht eine Beziehung zwischen der Brachymesophalangie und dem Mongolismus besteht.

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O. von Verschuer: **Wirksame Faktoren im Leben des Menschen.** Beobachtungen an ein- und zweieiigen Zwillingen durch 25 Jahre. Steiner Verlag, Wiesbaden 1954.

The purpose of this investigation was to determine to which extent individual changes of the physical and mental make up are linked to environment. The investigation was carried out on 150 pairs of twins of the same sex: 100 pairs were considered identical, 50 non-identical. At the beginning of the investigation between 1924 and 1925 the average age was 16 years: the majority of cases was below the age of 20. Each of the following age-groups contained roughly 30 pairs: 0–4, 5–9, 10–14 and 15–19 years. Repeated examinations were performed after 1 year, 11–12 years and 25–26 years. At the last examination about ⅔ of the primary material was seen.

In case of death the age at and cause of death were checked. The history of diseases, marriages and fertility were noted. The body build was recorded with the aid of about 20 anthropological measurements, mostly skeletal dimensions. The mental make up was observed during interviews and informally described.

The diagnostic principles of identity of twins are not described. The relatively great loss of the primary material (⅓) is evidently caused by World War II. Hence the results concerning life span and causes of death have to be judged with great caution. Furthermore this reduction of the material together with the war conditions will affect the representativeness of the final material.

The author distinguishes between environmental-stable and environmental-labile anthropometrical dimensions. Skeletal measurements are included in the first category, body-weight and thoracic measures in the last one. This infers that if one of the identical twins have larger values for a particular skeletal dimension at one occasion, he will also show a larger value than his twin at a later occasion. With regard to the body-weight, however, the dominance changes between the twins from time to time.

It is to regret that the intervals between the re-examinations are as long as 1 year, 10–11 years and 13–15 years respectively. This implies that information is lacking on the concordance concerning the growth rhythm both for various tissue components as for example the fat tissue (*cf.* Stoltz and Stoltz, Somatic Development of Adolescent Boys, New York 1951), and for various growth zones of the skeleton. Furthermore, the anthropometric methods are too unreliable to permit a more detailed comparison with the longitudinal growth studies from the last years (*cf.* Macy, Tanner, Björk). These objections are relevant also with regard to the changes of the adult body-build caused by the nutritional environment or the degree of physical activity. The variation of the body weight cannot be followed in their association with such environmental changes because of the long observational intervals.

It should be remarked that, during last years, there have been presented longitudinal investigations on twins as well as on non-related persons to show the association between environment and various mental or physical traits. The *duration* of these experiments are, however, adapted to the circumstances of a particular study. Thus, nutritional experiments are performed for some few months, which is also the case in studies on the alteration of body-build due to changed physical activity. Investigations of this kind are also utilized in longitudinal pharmacological experiments with very short duration (*cf.* Glass, Am. J. Human Genetics; 1954, *6*, 165).

The objections against the anthropometrical studies are relevant also as far as the study of the mental make up is concerned. The results are, however, not readily recognized

due to the methods applied, without the use of objective tests or in other way standardised norms.

As is shown above, it is not difficult to find objections against the investigations reported. In order to judge Verschuer's work with justice it should, however, be recognized that the investigations were planned and started about 1920. The principle of a longitudinal investigation is to repeat strictly the originally defined schedule of examination. Obviously the simultaneously conducted research during the observation period of 25 years must have led to new methodological aspects in the field under consideration. Furthermore some problems must at the same time lose their actuality or be solved in other ways. This makes it not very grateful to plan and perform such a longterm investigation. The author must be complimented on his patience to keep on the investigations in spite of these circumstances.

The outcome of the investigations or rather the knowledge gained by them is very slight, compared with the efforts put down by the investigator. This experience has perhaps a value of its own, suggesting that other methods might be tried to solve a problem where the present status of knowledge seems to indicate that longitudinal investigations would be suitable.   *Bengt Lindegård, Lund.*

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ÜBER DEN ZUSAMMENHANG ZWISCHEN AB0-BLUTGRUPPEN UND WEIBLICHEM GENITAL-CARCINOM

I. Auswertung der in Heidelberg erhobenen Befunde[1]

Von W. HELMBOLD, E. KRAH und H. BITZ

Das besonders in den letzten Jahren wieder vielfach untersuchte Problem eines möglichen Zusammenhanges zwischen den AB0-Blutgruppen und dem Auftreten bestimmter Erkrankungen hat inzwischen zu Ergebnissen geführt, welche die Fortsetzung dieser Arbeiten durchaus rechtfertigen. Insbesondere das von mehreren Autoren bestätigte Überwiegen der Blutgruppe 0 unter den Ulcus-pepticum-Patienten sowie das Überwiegen der Gruppe A bei Patienten mit Magen-Carcinom dürfte jetzt statistisch so gesichert sein, daß mit einem biologischen Zusammenhang gerechnet werden muß. Um welche Art von Pleiotropie es sich dabei handelt, ob um primäre oder sekundäre, ist jedoch noch völlig offen. Zusammenstellungen der bisherigen Ergebnisse sowie Literatur finden sich z.B. bei *Langmann* (1955), *Roberts* (1957), *Buckwalter* (1957), *Gianferrari* (1957) und *Prokop* (1958), sowie zum speziellen Problem bei *Krokfoss* und *Kinnunen* (1954), *Beolchini* und Mitarbeiter (I–III, 1956/57) und *Beolchini* und Mitarbeiter (1957).

Da vorläufig nichts über den Einzelfall ausgesagt werden kann, sondern Ergebnisse nur von großen Statistiken zu erwarten sind, sollten zumindest die bereits vorhandenen Unterlagen ausgenutzt und der Auswertung zugeführt werden. Je sicherer die statistischen Ergebnisse sind, desto eher wird

[1] Herrn Prof. Dr. E. Rodenwaldt zum 80. Geburtstag gewidmet.

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es möglich sein, von der allgemeinen Kenntnis von einem bestehenden Zusammenhang zwischen Blutgruppen und Krankheiten zur Erkenntnis der
spezifischen Ursachen und weiter vielleicht zu einer praktischen Auswertung im Interesse der Patienten zu kommen.

Auf Veranlassung von *O. Prokop* begann 1956 in Deutschland eine Materialsammlung über ein bisher wenig bearbeitetes Gebiet, nämlich über den
Zusammenhang zwischen AB0-Blutgruppen und weiblichem Genital-Carcinom, als deren Ergebnis bisher 11 Kliniker und Serologen Unterlagen zur
Auswertung einsandten. Sofern der Umfang des Einzelmaterials für sich
wesentliche Aussagen zuläßt, wird das jeweilige Ergebnis mit den einzelnen
Untersuchern veröffentlicht. Als Abschluß dieser Reihe wird das Gesamtergebnis für Deutschland unter Berücksichtigung der Beiträge aller Untersucher ausgewertet.

In vorliegender Arbeit wird über die Ergebnisse der Untersuchungen
über einen Zusammenhang zwischen Blutgruppen und weiblichem Genital-
Carcinom anhand der Befunde von Patientinnen Heidelberger Kliniken
berichtet.

Material und Methoden

Zur Verfügung standen die im Serologischen Institut Heidelberg durchgeführten Blutgruppenbestimmungen von Patientinnen und Kontrollpersonen aus der Medizinischen
Klinik, der Medizinischen Poliklinik, der Kinderklinik, der Frauenklinik (Patientinnen
und Nabelschnurblute), sowie aus den Blutbanken der Frauenklinik und der Chirurgischen
Klinik und aus dem Czerny-Krankenhaus.[1] In Tabelle 1 sind die Blutgruppenverteilungen
in den einzelnen Kliniken sowie die daraus resultierenden Genfrequenzen aufgeführt.
(Genfrequenzen nach Bernstein mit Korrektur. Varianzen bzw. mittlere Fehler sind hier
nicht angeführt, da sie für das Thema der Arbeit ohne Bedeutung sind. In die Heterogenitätsteste gehen sie mit ein.) P gibt die Übereinstimmungswahrscheinlichkeit von
Beobachtungs- und Erwartungswert wieder ($\chi^2 = 2N[1-r'\ p'q']D^2$; *Stevens* 1950).

Bei den Patienten des Czerny-Krankenhauses[1] handelt es sich um strahlenbehandelte
Personen mit vorwiegend malignen Neoplasmen. Sie kommen deshalb hier als Vergleichsgruppe nicht in Frage. Die Ca-Patientinnen stammen aus der Frauenklinik[1]. Es handelt
sich um 500 Patientinnen mit klinischer und histologischer Ca-Diagnose. In Tabelle 2
sind die entsprechenden Befunde aufgeschlüsselt.

Die statistische Auswertung vergleicht zunächst die Phänotypenfrequenzen oder die
Genfrequenzen der Blutgruppen in der Patientengruppe mit denen einer repräsentativen
Vergleichsgruppe. Diese Vergleichsgruppe soll das Normalkollektiv darstellen, von dem
sich die Patientengruppe nur durch die Erkrankung unterscheidet. Wichtig ist also die
genaue Prüfung der Normalblutgruppenverteilung; anderenfalls können an sich vorhandene Ergebnisse verdeckt oder sachlich nicht begründete als vorhanden vorgetäuscht
werden.

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[1] Den genannten Kliniken sei für die freundliche Überlassung des Materials verbindlichst
gedankt.

Tabelle 1

Die Blutgruppenverteilung in den verschiedenen Heidelberger Kliniken

Klinik		N	A	B	O	AB	p	q	r	P
1. Med. Klinik	1955	1443 abs.	596	158	604	85	0,27217	0,08771	0,64011	0,018
		%	41,30284	10,94941	41,85724	5,89051				
2. Med. Klinik	1956	1212 abs.	559	133	456	64	0,30271	0,08482	0,61246	0,78
		%	46,12211	10,97360	37,62376	5,28053				
3. Med. Klinik	1957	1605 abs.	761	156	633	55	0,29962	0,06822	0,63215	0,11
		%	47,41433	9,71963	39,43925	3,42679				
4. Med. Poliklinik	1955–1957	882 abs.	416	97	340	29	0,29742	0,07451	0,62808	0,045
		%	47,16553	10,99773	38,54875	3,28798				
5. Kinderklinik	1956	2354 abs.	1056	253	938	107	0,28876	0,07965	0,63159	0,88
		%	44,85981	10,74766	39,84707	4,54545				
6. Frauenklinik	1956	3649 abs.	1596	416	1472	165	0,28085	0,08311	0,63604	0,62
		%	43,73801	11,40038	40,33982	4,52179				
7. Nabelschnurblute	1955	1451 abs.	638	169	589	55	0,27795	0,08063	0,64141	0,13
		%	43,96968	11,64714	40,59269	3,79049				
8. Nabelschnurblute	1956	1749 abs.	769	170	729	81	0,28260	0,07441	0,64298	0,30
		%	43,96798	9,71984	41,68096	4,63122				
9. Blutbank Frauen	1955	786 abs.	338	91	330	27	0,26891	0,07834	0,65275	0,20
		%	43,00254	11,57761	41,98473	3,43511				
10. Blutbank Frauen	1956	1221 abs.	564	116	493	48	0,29394	0,06962	0,63643	0,73
		%	46,19165	9,50041	40,37674	3,93120				
11. Blutbank Frauen	1957	1236 abs.	579	118	494	45	0,29681	0,06838	0,63481	0,37
		%	46,84466	9,54692	39,96764	3,64078				
12. Blutbank Chirurgie	1955	659 abs.	298	63	268	30	0,29096	0,07316	0,63588	0,65
		%	45,22003	9,55994	40,66768	4,55235				
13. Blutbank Chirurgie	1956	1021 abs.	421	114	437	49	0,26499	0,08317	0,65183	0,47
		%	41,23408	11,16552	42,80117	4,79922				
14. Blutbank Chirurgie	1957	788 abs.	342	74	330	42	0,28289	0,07624	0,64087	0,095
		%	43,40101	9,39086	41,87817	5,32995				
15. Czerny-Krhs.	1955–1957	1976 abs.	971	205	723	77	0,31569	0,07433	0,60997	0,04
		%	49,13967	10,37449	36,58907	3,89676				

Tabelle 2
Die Blutgruppenhäufigkeiten unter den Ca-Patientinnen

Diagnose		N	A	B	0	AB	p	q	r	P
Gesamt-Ca		500 abs. %	249 49,80000	49 9,80000	177 35,40000	25 5,00000	0,32775	0,07697	0,59527	0,95
Collum-Ca	1)	360 abs. %	182 50,55555	41 11,38888	116 32,22222	21 5,83333	0,34048	0,09041	0,56911	0,76
Corpus-Ca	2)	94 abs. %	45 47,87234	5 5,31915	42 44,68085	2 2,12766				
Vulva + Vagina	3)	22 abs.	13	1	7	1				
Ovarial	4)	17 abs.	7	1	8	1				
Verschiedene	5)	7 abs.	2	1	4	–				
	2)–5)	140 abs. %	67 47,85714	8 5,71428	61 43,57143	4 2,85714	0,29768	0,04377	0,65854	0,82

Tabelle 3
Die Blutgruppenverteilung in den 3 Kontrollgruppen

Kontrollgruppe	N	A	B	0	AB	p	q	r	P
1) Blutbank Frauenklinik	2457 abs. %	1143 46,52014	234 9,52381	987 40,17094	93 3,78510	0,29538	0,06899	0,63562	0,38
2) Frauenklinik + Blutbank Chirurgie	6117 abs. %	2657 43,43632	667 10,90404	2507 40,98414	286 4,67549	0,27952	0,08115	0,63933	0,53
3) Kinderklinik + Nabelschnurblute	5554 abs. %	2463 44,34641	592 10,65898	2256 40,61937	243 4,37522	0,28398	0,07825	0,63776	0,76

Um Maximum-Likelihood-Werte zu erhalten, können mathematisch für den Vergleich die von *Stevens* (1950) beschriebene Methode oder die von *Woolf* (1955) (auch bei *Race* und *Sanger*, 3. Aufl. 1958) benutzt werden. Bei der ersten Methode werden die aus den Stichproben errechneten Genfrequenzen miteinander verglichen, wobei für den Vergleich zweier Stichproben die Beziehung gilt:

$$\chi^2 = \frac{N_1\,N_2}{N_1 + N_2}\,(i_{pp}\,\delta p^2 + 2\,i_{pq}\,\delta p\,\delta q + i_{qq}\,\delta q^2)$$

(*Stevens* 1950. Näheres über die Berechnung der Informationen i auch bei *Helmbold* und *Prokop* 1958.)

Nach *Woolf* werden die absoluten Beobachtungszahlen zweier Phänotypen (oder Phänotypengruppen) miteinander verglichen, wobei der Quotient x = hK/kH die relative Häufigkeit des Auftretens der Erkrankung bei den Trägern der einen Blutgruppe im Verhältnis zu der anderen Blutgruppe angibt. h und k bedeuten dabei die Anzahl der Träger der jeweiligen Merkmale (z.B. A und 0) bei den Patienten, H und K die entsprechenden Werte für die Kontrollgruppe. Nach logarithmischer Transformation von x erhält man y = ln x (= $\log_e$ x). Die Stichprobenvarianz von y ist V = 1/h + 1/k + 1/H + 1/K. Das Gewicht von y ist dann w = 1/V. Zur Prüfung der Nullhypothese ist χ^2 = wy² mit einem Freiheitsgrad.

Die normale AB0-Verteilung

Die Auswahl einer normalen Vergleichsgruppe über die AB0-Verteilung stieß in Heidelberg auf besondere Schwierigkeiten. Mit einer großen Heterogenität mußte auf Grund der Bevölkerungsstruktur gerechnet werden (starke Bevölkerungsverschiebungen infolge der Kriegs- und Nachkriegsereignisse, größerer Anteil nicht einheimischer Studenten). Die Homogenitätsteste bestätigen diese Vermutung: Es bestehen Unterschiede zwischen den einzelnen Kliniken, zum Teil auch innerhalb der Kliniken für die einzelnen Jahre (Differenzen statistisch signifikant oder an der Signifikanzgrenze). Einzelne Stichproben zeigen eine derartig hohe Heterogenität, daß sie als Normalkontrolle nicht in Frage kommen.

Aus den Homogenitätstesten ergaben sich schließlich 3 Stichproben, welche den Ca-Fällen gegenübergestellt werden können:

1) Blutbank Frauenklinik 1956/57,
2) Frauenklinik 1956 + Blutbank Chirurgie 1955–1957, und
3) Kinderklinik 1956 + Nabelschnurblute 1955/56.

Die Blutgruppenhäufigkeiten und Genfrequenzen sind in Tabelle 3 aufgeführt. Die Stichprobe 1) der Tabelle unterscheidet sich signifikant von den beiden anderen: Mit einem P von 0,002 von Stichprobe 2) und einem

P von 0,032 von Stichprobe 3). 2) und 3) unterscheiden sich statistisch
nicht voneinander (P = 0,51). Dieser Befund läßt auf Grund der Heidel-
berger Verhältnisse die Deutung zu, daß die Blutgruppenverteilung der ein-
heimischen Heidelberger Bevölkerung durch die Patienten der Frauenklinik
und Spender der Blutbank Chirurgie sowie durch die Patienten der Kinder-
klinik und durch die Nabelschnurblute vertreten wird, während sich die
Spender der Blutbank Frauenklinik in beträchtlichem Umfang aus nicht
in Heidelberg beheimateten Personen zusammensetzen.

Die Personen, welche Blut spenden, stammen bei der in der Stadt ge-
legenen Frauenklinik mehr aus Gelegenheitsspendern (Studenten usw.),
bei der Chirurgischen Klinik, welche ziemlich isoliert auf der anderen Neckar-
seite liegt, dagegen mehr aus Angehörigen der Patienten. Erfahrungsgemäß
betreffen größere chirurgische Eingriffe, für welche eine Transfusionspro-
phylaxe und damit eine Blutgruppenbestimmung durchgeführt wird, mehr
fest in der Umgebung der betreffenden Klinik ansässige Patienten. Des-
gleichen wird das Ereignis einer Entbindung mehr ortsansässige Frauen
betreffen, so daß die Kinder und Säuglinge ebenfalls am ehesten die ein-
heimische Bevölkerung vertreten. Für diesen Gedankengang spricht auch
die Tatsache, daß die beiden Stichproben 2) und 3) statistisch nicht diffe-
rieren und die Stichprobenheterogenitäten mit P = 0,53 bzw. P = 0,76
sich durchaus im normalen Bereich bewegen. (Diese beiden Stichproben
dürfen jedoch nicht zusammengelegt werden, da 3) im wesentlichen Kinder
der Frauen von 2) und damit nicht unabhängig sind.)

Da es sich bei den Ca-Patientinnen im wesentlichen um in Heidelberg
und Umgebung beheimatete Frauen handelt, die außerdem ebenfalls von
der Frauenklinik erfaßt wurden, darf nach dem oben Gesagten der durch
die Stichproben 2) und 3) (Tabelle 3) erfaßte Personenkreis als am besten
begründete Normalbevölkerung den Ca-Patienten gegenübergestellt werden.

Die relative AB0-Verteilung unter den Ca-Patientinnen

Vergleicht man die Blutgruppenfrequenzen der Ca-Patientinnen mit
denen der Vergleichsgruppen, so ergibt sich das in Tabelle 4 dargestellte
Bild. Danach unterscheidet sich die Kontrollgruppe 1) zwar nicht signi-
fikant von den Ca-Patientinnen, doch besteht bei einem P von 10% der
Verdacht, daß eine Vergrößerung der Stichprobe zur Signifikanz führen
könnte. Zu Gruppe 2) ist dagegen die Differenz hoch signifikant, zu Kon-
trollgruppe 3) ebenfalls noch sicher signifikant.

Prüft man die größte Gruppe der Ca-Patientinnen, die Gruppe der
Collum-Carcinome ($5,0\%$ Adeno-Ca, Rest Plattenepithel-Ca), gegen die

Tabelle 4

Die P-Werte für den Vergleich Kontrollgruppen / Ca-Gruppen

Kontrollgruppe geprüft gegen:	Gesamt-Ca	Collum-Ca
1) Blutbank Frauenklinik	P = 0,10	P = 0,004
2) Frauenklinik + Blutbank Chirurgie	P = 0,0075	P = 0,002
3) Kinderklinik- und Nabelschnurblute	P = 0,024	P = 0,003

Kontrollen, so ergibt sich überraschend, daß trotz Verkleinerung der Stichprobe eine wesentlich höhere Signifikanz erhalten wird (Tabelle 4). Das bedeutet also, daß im vorliegenden Material die Verschiebung der Blutgruppenhäufigkeiten unter den Ca-Patientinnen gegenüber der Normalbevölkerung durch die Blutgruppenfrequenzen unter den Collum-Ca-Patientinnen gegenüber den übrigen Ca-Patientinnen bedingt ist. Eine Prüfung der Collum-Ca- gegen die übrigen Ca-Patientinnen ergibt bei Anwendung der *Stevens*schen Methode ein Heterogenitäts- χ^2 von 8,5 (P = 0,018), also eine ausreichende Signifikanz. Dabei trägt die Differenz der q-Werte (Gen B) mit dem größten, für sich signifikanten χ^2, zu der Gesamtsignifikanz bei. Die p-Differenzen (Gen A) sowie die Differenzen zwischen den Phänotypen (A gegen 0 nach *Woolf* geprüft) sind für sich nicht signifikant.

Trotz der relativ kleinen Stichproben ergänzen diese Teste den Befund, daß für die Abweichung der AB0-Frequenzen der Ca-Patientinnen von der Kontrollpopulation die Gruppe der Collum-Ca-Patientinnen verantwortlich ist.

Die oben genannten Vergleiche wurden anhand der Genfrequenzen nach der *Stevens*schen Methode durchgeführt. Als Ursache für die Differenzen zwischen Kontrollen und Ca-Patientinnen erwies sich eine bei den Ca-Patientinnen signifikant erhöhte Genfrequenz p (Gruppe A). Die Differenzen der p-Werte zwischen den 3 Kontrollgruppen und den beiden Ca-Gruppen (Gesamt-Ca, Collum-Ca) ergaben folgende χ^2-Werte (FG = 1):

Kontrolle 1) gegen Gesamt-Ca 3,29; gegen Collum-Ca 5,14
Kontrolle 2) gegen Gesamt-Ca 9,12; gegen Collum-Ca 10,72
Kontrolle 3) gegen Gesamt-Ca 7,35; gegen Collum-Ca 9,03

Die hohe Signifikanz der Gesamtdifferenz zwischen Kontrollgruppe 1) (Blutbank Frauenklinik 1956/57) und Collum-Ca (Tabelle 4) ist durch die nur hier zusätzlich vorhandene Differenz zwischen den beiden q-Werten bedingt, welche ein χ^2 von 4,35 ergibt. Der Vergleich der Collum-Ca-Fälle

mit Kontrolle 1) zeigt demnach eine signifikante Erhöhung von p und q auf Kosten von r bei den Ca-Fällen, während die anderen Vergleiche nur eine Erhöhung von p bei den Ca-Fällen ergeben.

Von der Erhöhung der Genfrequenz von A (p) bei den Ca-Patientinnen läßt sich wieder an die eingangs gestellte Frage anknüpfen, um welche Art von Pleiotropie es sich bei den Zusammenhängen zwischen Blutgruppen und Krankheit handelt, ob es sich um direkte genetische Mechanismen oder um physiologische oder pathologische Wirkungen der Blutgruppensubstanzen selbst handelt. Um Anhaltspunkte dafür zu gewinnen, wäre z.B. auf die Häufigkeitsreihenfolge des Ca-Befalls in bezug auf die einzelnen AB0-Phänotypen zu prüfen.

Der Quotient x der *Woolf*schen Methode ist ein sehr eindrucksvoller Maßstab für die Ca-Häufigkeit innerhalb einer Blutgruppe gegenüber einer anderen. In Tabelle 5 sind die x-Werte für die einzelnen Vergleiche angegeben, wobei die signifikanteste Ca-Gruppe, die Collum-Carcinome, den beiden Vergleichsgruppen 2) und 3) der Tabelle 3 gegenübergestellt wurden. P gibt die Wahrscheinlichkeit für die Signifikanz der Differenz an.

Tabelle 5

Die x- und P-Werte für den Blutgruppenvergleich zwischen Collum-Ca-Patientinnen und Kontrollgruppen 2) und 3)

Blutgruppenvergleich gegen: Kontrolle 2)			Kontrolle 3)	
AB : 0	x = 1,58	P = 0,067	x = 1,68	P = 0,035
A : 0	x = 1,48	P = 0,0013	x = 1,44	P = 0,003
B : 0	x = 1,33	P = 0,13	x = 1,34	P = 0,12
A : B	x = 1,11	P = 0,54	x = 0,93	P = 0,21
AB : A	x = 1,07	P - 0,76	x = 1,17	P - 0,52
AB : B	x = 1,19	P = 0,52	x = 1,25	P = 0,43

Auffallend ist wieder die hohe Signifikanz der größeren Ca-Häufigkeit unter den Patientinnen der Gruppe A gegenüber denen der Gruppe 0. Die Differenz zwischen den Patientinnen der Gruppe AB und 0 bewegt sich an der Signifikanzgrenze, während die zwischen B und 0 nicht sicher ist.

Interessant ist die für beide Kontrollgruppen parallel gehende Reihenfolge der Größe von x: Nach diesen Ergebnissen ist die Ca-Häufigkeit unter den Patientinnen der Blutgruppe AB am höchsten, dann folgen die Gruppen A, B und natürlich 0.

Abschließend sei noch auf die ABO-Verteilung unter den Patienten des Czerny-Krankenhauses eingegangen. Die 3 Jahrgänge waren untereinander homogen, so daß sie zu der in Tabelle 1 angegebenen Stichprobe Czerny-Krankenhaus 1955–1957 zusammengefaßt werden durften. Da es sich vorwiegend um strahlenbehandelte Patienten mit malignen Neoplasmen handelt, konnte diese Stichprobe nicht als normale Kontrollgruppe verwendet werden. Es handelt sich um Neoplasmen verschiedener Lokalisation, so daß diese Stichprobe zum Thema weibliche Genitalcarcinome und ABO-Blutgruppen keine Information geben kann. Allgemein ergab sich jedoch auch hier eine signifikant größere Häufigkeit der Gruppe A unter den Patienten gegenüber den Normalkontrollen 2) und 3) der Tabelle 3. Die P-Werte betrugen im A/0-Vergleich nach *Woolf* mit den Kontrollen 2) und 3) 0,00003 bzw. 0.0003 (x = 1,26 bzw. 1,23), also eine außerordentlich gute Sicherung. Im Homogenitätstest mit den 500 Ca-Patientinnen ergaben die Patienten des Czerny-Krankenhauses eine P von 0,6; es besteht demnach keine statistische Differenz in der Blutgruppenverteilung. Diese beiden Stichproben wurden nun zusammengelegt und gegen die Normalkontrollen geprüft. Die Signifikanz im A/0-Vergleich ließ sich auf P = 0,0000025 gegenüber Kontrolle 2) (Tab. 3) bzw. P = 0,00004 gegenüber Kontrolle 3) steigern! Dies besagt, daß unter den hier untersuchten Patienten mit Neoplasmen die Gruppe A mit nahezu absoluter Sicherheit häufiger ist, als der normalen ABO-Verteilung entspricht.

Die AB/0-, B/0-Vergleiche, entsprechend der Tabelle 5, ergaben mit diesem Gesamtmaterial (500 Ca-Patientinnen + Czerny-Krankenhaus) keine größere Tumor-Häufigkeit bei den Patienten der Gruppen B und AB gegenüber denen der Gruppe 0. Die x-Werte lagen zwischen 1,006 und 1,07, die P-Werte zwischen 0,4 und 0,9; die für die Collum-Ca-Patientinnen beobachtete Häufigkeitsreihenfolge (Tabelle 5) ließ sich demnach hier nicht nachweisen.

Diskussion

Die ABO-Verteilung in einer Stichprobe von 500 Genital-Ca-Patientinnen erwies sich nach den angeführten statistischen Testen als signifikant verschieden von der Verteilung in der Normalbevölkerung. Dabei konnte nachgewiesen werden, daß diese Verschiebung der ABO-Verteilung durch die Gruppe der Collum-Ca-Patientinnen bedingt ist. Ursächlich ist eine Erhöhung der A-Genfrequenz (p) bei den Ca-Patientinnen. Ob die gegenüber einer Kontrollgruppe beobachtete Erhöhung der B-Genfrequenz (q) von

Bedeutung oder nur ein Zufallsbefund ist, läßt sich vorläufig nicht ent-
scheiden, zumal diese Kontrollgruppe nicht die Heidelberger Bevölkerung
repräsentiert, aus der die Ca-Patientinnen stammen. Als logisch und stati-
stisch am besten begründete Vergleichs-Normalbevölkerung erwiesen sich die
Stichproben aus der Frauenklinik + Spender der Blutbank Chirurgie so-
wie die Patienten der Kinderklinik + Nabelschnurblute (Säuglinge).

Diese Heterogenitätsteste wurden zwar mittels der Blutgruppengen-
frequenzen aus den einzelnen Stichproben durchgeführt, doch dürfen die
erhaltenen Differenzen noch nicht dahin gedeutet werden, daß die Bezie-
hungen der AB0-Blutgruppen zum Carcinom direkt blutgruppen-bedingt
sind. Es ist zwar durchaus möglich, daß die AB0-Blutgruppengene außer
für die Ausprägung der betreffenden Blutgruppeneigenschaften auch direkt
oder indirekt für die Ca-Empfindlichkeit verantwortlich sind, doch können
Beweise dafür bisher nicht erbracht werden. Eine Gendosiswirkung, welche
dann vielleicht zu erwarten wäre, läßt sich aus unseren Daten nicht ablesen.
Wie Tabelle 5 zeigt, ist der x-Wert für die Heterozygoten (AB) größer als
der für die Heterozygoten + Homozygoten (A). Wie auch der Vergleich
AB/A zeigt, läßt sich zwischen der Ca-Empfindlichkeit dieser beiden Grup-
pen kein Unterschied nachweisen.

Ob die Ursachen für die hier festgestellte Ca-Häufigkeitsreihenfolge
(AB–A–B–0) wirkliche Bedeutung haben, läßt sich erst entscheiden, wenn
darüber weiteres Material vorliegt. Die von *Aird* (1955) geäußerte Hypo-
these, daß es sich bei dem Zusammenhang zwischen Blutgruppen und Ca
nicht um eine höhere Empfindlichkeit einzelner Bluttypen, sondern eher
um eine Schutzwirkung der Blutgruppenmucopolysaccharide handelt, wo-
bei die Substanzen 0 und B im Vergleich zu A relativ wirksamer gegen
Krebs schützen, scheint durch die angeführte Häufigkeitsverteilung eine
Stütze zu erhalten.

Unsere Ergebnisse für das Collum-Carcinom lassen sich durchaus mit
einer Schutzwirkung der Gruppe 0 interpretieren; falls B auch eine Schutz-
wirkung hat, dann jedoch sicher wesentlich geringer als Gruppe 0. Danach
weist die Blutgruppe ohne 0-Anteil, AB, die höchste Ca-Frequenz auf, nach-
folgend die Gruppe A mit dem höchsten Homozygotenprozentsatz, danach
die Gruppe B mit geringem Homozygotenanteil und schließlich die Gruppe
0. Eine ausführliche Diskussion dieser oder anderer möglichen Hypothesen
halten wir jedoch noch für verfrüht. Genauere Analysen setzen weitere
Daten voraus.

Die Befunde für die Patienten des Czerny-Krankenhauses liefern eine
außerordentlich gut gesicherte Bestätigung dafür, daß die Häufigkeit der
Gruppe A unter Patienten mit malignen Neoplasmen erhöht ist. Im Gegen-

satz zu den Ergebnissen bei den Collum-Ca-Patientinnen tritt hier nicht die in Tabelle 5 dargestellte Häufigkeitsreihenfolge (AB–A–B–0) auf. Die Tumor-Häufigkeit ist bei den Patienten der Gruppe AB, B und 0 gleich hoch, nur die Gruppe A zeigt eine höhere Tumor-Häufigkeit von nahezu absoluter Signifikanz. Wie weit sich hier prinzipielle Unterschiede zwischen den verschiedenen Neoplasmen-Typen und ihrem Verhältnis zu den ABO-Blutgruppen abzeichnen, kann noch nicht entschieden werden.

Zusammenfassung

Die ABO-Blutgruppenverteilung in einer Stichprobe von 500 Genital-Ca-Patientinnen wurde mit der Verteilung in der Normalbevölkerung verglichen. Es konnte ein signifikantes Überwiegen der Gruppe A bzw. der Genfrequenz p unter den Patientinnen nachgewiesen werden. Verantwortlich für diese Abweichung von der Kontrollverteilung war im wesentlichen die Gruppe der Collum-Ca-Patientinnen.

Bei einer weiteren Stichprobe von Patienten mit malignen Neoplasmen ließ sich ein statistisch signifikanter Überschuß an Patienten der Gruppe A nachweisen.

Summary

When the ABO blood group frequencies of 500 female patients with carcinoma of the genital system were compared with those observed in a normal population sample, significant differences were noted. An increase of blood group A was found, especially among patients with carcinoma of the cervix.

Résumé

Chez cinq cents malades atteints de carcinome génital la distribution des groupes sanguins ABO a été examinée. On a trouvé un excès significatif du groupe A, c'est-à-dire de la fréquence p du gène en question vis-à-vis de la population en général. Cet excès du groupe A est surtout dû au groupe des malades atteints d'un Ca du col. Dans une autre série de malades atteints de néoplasme malin on a également constaté un excès significatif du Ca.

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ABO BLOOD GROUPS IN STOMACH CANCER*)

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Since *Aird* (1953) in Britain demonstrated an association between ABO blood groups and stomach cancer, group A being significantly more common in patients with stomach cancer than in controls, several contributions from all over the world have thrown more light on the question.

Table 1, giving a survey of the results published up to now, shows that almost all authors have found a significantly higher incidence of blood group A among patients with stomach cancer.

Billington in Sidney, Australia, found there was no overall association between blood group A and carcinoma of the stomach in a group of 483 patients; but when the gastric carcinoma group was sub-divided according to site, prepyloric and cardiac lesions were found to be significantly associated with blood group A, whereas body and fundus lesions were associated with blood group O.

Material

The aim of the present investigation was to analyse the ABO blood groups among a group of patients with stomach cancer in relation to sex, age, localization, histological diagnosis, and stomach acidity. The material includes 1,764 patients, viz. 1,106 males and 658 females consecutively admitted to Copenhagen Hospitals during the period 1945–1957. The diagnoses were verified according to the usual criteria. Most of the cases were operated on, or an autopsy was made with a microscopic examination; a few cases were verified by characteristic X-ray findings only; all doubtful cases have been omitted.

Table 1

ABO blood group distribution in percentages in patients with stomach cancer
and in controls

Author	No. of patients	Blood type	Control per cent	Gastric cancer, per cent	Diff. in per cent from control
Aird & al.	3 632	O	48.6	44.5	—4.1
		A	39.8	44.8	5.0
		B	8.3	7.8	—0.5
		AB	3.2	2.9	—0.3
Holländer	704	O	41.6	36.2	—5.4
		A	45.1	53.1	8.0
		B	9.0	7.5	—1.5
		AB	4.3	3.2	—1.1
Køster & al.	413	O	40.6	34.1	—6.5
		A	44.0	51.3	7.3
		B	10.9	10.7	—0.2
		AB	4.5	3.9	—0.6
Buckwalter & al.	908	O	45.8	42.2	—3.6
		A	41.6	45.8	4.2
		B	9.0	9.2	0.2
		AB	3.6	2.8	—0.8
Jordal	385	O	40.6	38.4	—2.2
		A	44.0	50.6	6.6
		B	10.9	8.1	—2.8
		AB	4.5	2.9	—1.6
Beolchini & al.	678	O	42.9	38.64	—4.24
		A	41.8	48.23	6.41
		B	10.0	9.29	—0.73
		AB	5.8	3.84	—1.44
Billington	483	O	48.91	47.8	—1.11
		A	38.38	40.0	1.62
		B	9.70	7.2	—0.4
		AB	3.01	5.0	
Hogg & Pack	237	O	44.16	34.6	
		A	40.45	43.5	3.05
		B	10.03	13.0	
		AB	5.37	8.5	

Results

Table 2 gives the blood-group distribution in the patient group. As
controls, the material of *Bryde Andersen* was used. He analysed the blood-
group distribution in 14 304 healthy persons in Copenhagen.

It is seen from this table that blood group A occurs more and blood group O less frequently than in the controls. The differences are statistically significant ($\chi^2 = 13.3$; d.f. $= 3$).

Table 2

ABO blood-group distribution in 1 764 patients (author's material) with stomach cancer and in 14 304 controls

Blood group	Patients	Controls	Total
A	854	6 299	7 153
O	673	5 804	6 477
B	172	1 557	1 729
AB	65	644	709
Total	1 764	14 304	16 068
	per cent	per cent	per cent
A	48.4	44.0	44.5
O	38.2	40.6	40.3
B	9.8	10.9	10.8
AB	3.7	4.5	4.4
Total	100.1	100.0	100.0

Table 3

Distribution of ABO blood-groups within the different age groups of 1 764 patients within stomach cancer

Blood group	age —49	age 50—59	age 60—69	age 70—79	Total
A	113	189	312	240	854
O	91	153	243	186	673
B + AB	26	64	82	65	237
Total	230	406	637	491	1 764
	per cent	per cent	per cent	per cent	per cent
A	49.1	46.6	49.0	48.9	48.4
O	39.6	37.7	38.1	37.9	38.2
B + AB	11.3	15.8	12.9	13.2	13.4
Total	100.0	100.1	100.0	100.0	100.0

When the material is compared with the blood-group distribution found in other stomach-cancer patients from Copenhagen reported earlier by *Køster* and by *Jordal*, there is no statistically significant difference between the materials. The increased incidence of blood group A and the decreased incidence of blood group O in stomach-cancer patients is thus confirmed in a total of 2,562 patients from the Copenhagen area.

Woolf introduced a method of estimating the relationship between blood group and disease by giving incidence rates for the various blood groups, thus avoiding the spurious heterogeneity that differences in blood-group frequencies in the population introduce.

The incidence rate in the present material is 1.17 (with 95% fiducial limits: 1.28–1.06), which means that patients with blood group A run 17% more risk of getting stomach cancer.

The material is analysed in relation to four age groups and three blood types (B and AB blood groups are taken together). It is seen from *Table 3* that there is no significant difference in the distribution of the blood groups within the different age groups. [($\chi^2 = 10.9$; d.f. $= 8$). The χ^2 test is based on a break-down analysis of male and female patients.]

Table 4 shows that there is no difference in the ABO blood-group distribution in male and female patients with stomach cancer. [($\chi^2 = 10.5$; d.f. $= 12$). The χ^2 test is based on a break-down analysis in age groups.]

Table 4

Distribution of ABO blood-groups in 1 764 male and female
patients with stomach cancer

Blood group	number of males	number of females	Total
A	525	329	854
O	439	234	673
B + AB	142	95	237
Total	1 106	658	1 764
	per cent	per cent	per cent
A	47.5	50.0	48.4
O	39.7	35.6	38.2
B + AB	12.8	14.4	13.4
Total	100.0	100.0	100.0

In the following analysis of the material, then, no regard is paid to the sex and age distribution of the patients.

Table 5 shows the ABO blood-group distribution in relation to the site

Table 5

ABO blood-group distribution in 1 739 patients with stomach cancer, in relation to the localization of the tumour

Blood group	prepyloric	body	cardia	all stomach	total
A	387	271	105	78	841
O	311	203	83	68	665
B + AB	117	70	22	24	233
Total	815	544	210	170	1 739
	per cent	per cent	per cent	per cent	per cent
A	47.5	49.8	50.0	45.9	48.4
O	38.2	37.3	39.5	40.0	38.2
B + AB	14.4	12.9	10.5	14.1	13.4
Total	100.1	100.0	100.0	100.0	100.0

Table 6

ABO blood-group distribution in 1 728 patients with stomach cancer, grouped according to histological diagnosis

Blood group	Adeno-carcinoma	Carcinoma solidum	Scirrous and carcinoma anaplasticum	No histological diagnosis	Total
A	317	133	68	321	839
O	255	91	61	251	658
B + AB	78	37	17	99	231
Total	650	261	146	671	1 728
	per cent	per cent	per cent	per cent	per cent
A	48.8	51.0	46.6	47.8	48.6
O	39.2	34.9	41.8	37.4	38.1
B + AB	12.0	14.2	11.6	14.8	13.4
Total	100.0	100.1	100.0	100.0	100.1

of the tumour. As information is lacking abou. 25 patients, the total material comprises 1,739 patients. The table shows that in the present material there is no correlation between the blood-type distribution and the localization of cancer ($\chi^2 = 11.8$; d.f. $= 12$).

Table 7

ABO blood-group distribution in 1 764 patients with stomach cancer, in relation to earlier peptic ulcer or ulcer symptoms

Blood group	Verified peptic ulcer	Previous peptic ulcer symptoms	No peptic ulcer symptoms	No information	Total
A	53	89	600	112	854
O	40	76	450	107	673
B + AB	20	29	160	28	237
Total	113	194	1 210	247	1 764
	per cent	per cent	per cent	per cent	per cent
A	46.9	45.9	49.6	45.3	48.4
O	35.4	39.2	37.2	43.3	38.2
B + AB	17.7	14.9	13.2	11.3	13.4
Total	100.0	100.0	100.0	99.9	100.0

Table 8

ABO blood-group distribution in 1 764 patients with stomach cancer, classified according to information about gastric acidity

Blood group	achlorhydria	free acid present	no information	total
A	283	125	446	854
O	229	92	352	673
B + AB	76	35	126	237
Total	588	252	924	1 764
	per cent	per cent	per cent	per cent
A	48.1	49.6	48.3	48.4
O	38.9	36.5	38.1	38.2
B + AB	12.9	13.9	13.6	13.4
Total	99.9	100.0	100.0	100.0

Table 6 shows that there is no correlation between the ABO blood-group distribution and the histological diagnosis of the cancer ($\chi^2 =$ 12.8; d.f. = 12).

It is seen from *Table 7* that there is no difference in the distribution of blood groups in patients with stomach cancer, grouped according to whether they had 1) earlier verified peptic ulcer, 2) anamnestic symptoms giving suspicion of peptic ulcer, but not verified, and 3) no earlier ulcer symptoms.

In *Table 8* the ABO distribution is given in relation to gastric acidity. There is no statistically significant difference as to the type distribution in the patient groups with 1) achlorhydria, 2) free acid present, and 3) no information about gastric acidity.

As regards 1,165 patients there is information about rhesus blood groups. A statistical analysis failed to reveal any difference in the rhesus blood groups of the stomach-cancer patients, when they were grouped according to sex, age, and the different characteristics of the tumour.

Discussion

The increased frequency of blood group A in patients with stomach cancer has been confirmed in the present material, but the reason why persons with blood group A run 17% more risk of getting stomach cancer is still not clear.

The fact that similar results have been recorded in so many parts of the world makes it very unlikely that the association between ABO blood groups and stomach cancer should be simply due to chance; for the same reason, there is no great likelihood that the relationship might be due to anthropological factors explained by stratification of the population.

It seems most reasonable, then, to assume that the blood-group substances, owing to their presence in gastric mucosa and in gastric secretion, are factors either in the production of, or the protection against stomach cancer *(Bentall)*.

Billington's finding, relating the blood-group distribution to the site of the lesion, presented an interesting new aspect. But his findings could not be confirmed in the present material, although the number of patients included was four times bigger. No difference could be found as to the blood-group distribution in patients with different localizations of stomach cancer. There is no evident explanation for this discrepancy.

The blood-group distribution in stomach cancer patients who have had earlier ulcer symptoms did not reflect the established increased frequency of blood group O in patients with duodenal ulcer, probably because the

material is small and includes mostly patients with earlier stomach ulcer.

It was perhaps to be expected that a difference might be found as to blood-group distribution between the patients with achlorhydria and the patients with free acid present, because *Køster* found in patients with stomach lesions that the shift from conditions associated with the greatest production of acid is accompanied by an increasing frequency of blood group O and decreasing frequency of blood group A. More material is needed for a further elucidation of this question, however.

Among patients with pernicious anemia, as well as among patients with stomach cancer, there is the same correlation to blood group A (16).

This is remarkable in view of the fact that patients with pernicious anemia run 3–4 times more risk of developing stomach cancer than the general population does (12); moreover in pernicious anemia, and probably in stomach cancer also, there is evidence that genetic factors are active in the etiology (11, 14).

Summary

Increased frequency of blood group A has been confirmed in a group of 1,764 patients with stomach cancer. For further analysis the material was sub-divided according to sex, age, histological diagnosis, site of the tumour, information about earlier peptic ulcer, and information about gastric acidity. No differences, however, were found between the percentage distribution of the blood types in these groups.

Zusammenfassung

Bei einer Gruppe von 1764 Patienten mit Magenkrebs konnte eine Vermehrung der Blutgruppe A bestätigt werden. Für eine eingehendere Analyse wurde das Material aufgegliedert nach Geschlecht, Alter, histologischer Diagnose, Lokalisation des Tumors, Information über früheres Auftreten peptischer Ulcera und Information über die Acidität des Magensaftes. In der prozentualen Verteilung der Blutgruppen in diesen Untergruppen wurden jedoch keine Unterschiede gefunden.

Résumé

En examinant 1764 cas malades atteints de cancer de l'estomac, il a été possible de confirmer l'augmentation de la fréquence du groupe A. En vue

d'une analyse plus détaillée, le matériel a été classé selon le sexe, l'âge, le diagnostic histologique, la localisation de la tumeur, l'indication anamné- sique concernant les ulcères peptiques antérieurs et l'acidité gastrique. Toutefois, aucune différence concernant la fréquence des groupes sanguins dans ces différents groupes n'a pu être établie.

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SEX-LINKED CONGENITAL DEAFNESS

By R. DERAEMAEKER, Antwerp

As a result of extensive research work it is well established now that in most instances hereditary congenital deafness is due to one of a few autosomal recessive genes and that in general a slight preponderance of male cases is found. Although this seems to be the general rule, it is known that in addition there exists a type of congenital deafness that is due to a sex-linked recessive gene. This was established beyond doubt by *Sataloff et al.* in 1955 and recently confirmed by *Parker* (1958).

Though it might help to explain the slight preponderance of male cases, the discovery of a sex-linked gene for congenital deafness also complicates the situation. A sporadic male case may as well be due to an autosomal recessive as to a sex-linked recessive gene, and even if we find more than one male case in the family, it may not be easy to decide whether an autosomal or a sex-linked recessive gene is responsible. It seems, however, that the sex-linked type is so rare that in most instances an autosomal recessive gene should be accepted as the cause of the impaired hearing.

While studying the occurrence of hereditary congenital deafness in the province of Antwerp, we met a family in which the deafness may well be due to a sex-linked gene. A subsequent search in the literature disclosed another family that may belong to the same group.

The Pedigrees

Fig. 1 which represents the pedigree of family De B., shows that three of the members were deaf: II, 7, born in 1888 and deceased in 1942, was profoundly deaf since birth and mentally deficient; III, 4 was born deaf in 1909 and is able to speak only a few words; he went to a school for the deaf but with poor results as he too was mentally deficient, although far less than his uncle II, 7; the propositus IV, 8 was born deaf in 1936 and has little intelligible speach; he is physically normal but mentally slightly deficient.
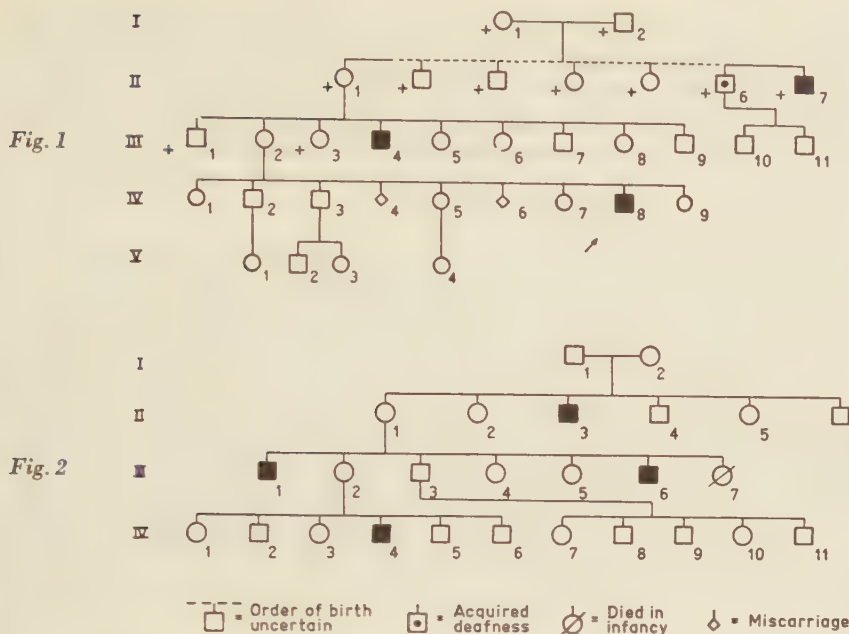
Fig. 1 – Pedigree of family De B.

Fig. 2 – Part of pedigree HD 3 (Stevenson and Cheeseman, Ann. hum. Genet. 20)

As far as could be detected no disease, intoxication or injury can be held responsible for the deafness in the cases just mentioned. The other members of the family are or were all normal in every respect, except II,6 who became deaf at the age of six after an unspecified illness. It should be noted that the mother of the propositus has had two miscarriages, one of four months, the other of about three months.

The family discovered in the literature was described by *Stevenson* and *Cheeseman* (1956) and appears in their paper under the pedigree reference number HD 3. There were four male cases of congenital deafness and the mode of inheritance strongly suggests a recessive sex-linked gene (Fig. 2) although the authors seem to assume autosomal inheritance.

Discussion

The families described by *Sataloff et al.* and by *Parker* undoubtedly indicate a sex-linked type of hereditary deafness. In both the deafness manifested itself in male children and was transmitted through the maternal side; the female case of deafness (*Parker*) seems to be the result of a union

between a deaf male and his sister who was evidently heterozygote for the gene. The number of deaf members and their distribution over a number of generations make these two families excellent "text-book" examples of sex-linkage. In practice, however, the families are generally much smaller and do not include as many cases as those mentioned above. Therefore, it may be difficult to reach a firm conclusion about the way the disease is transmitted in such families.

In both families described in this paper, deafness was restricted to male children and the gene was transmitted through a healthy female who has at least one deaf brother. This favours the assumption of a sex-linked recessive gene but does not rule out the possibility of simple autosomal inheritance. The statistical analysis shows that the ratio of 35 normal to 7 affected members is statistically compatible with the 3:1 expectation in autosomal recessive inheritance ($X^2 = 1,554$; 1 d.f.; $0.3>P>0.2$). The sex distribution, however, is not: we should expect 15.75 normal and 5.25 affected female members and we find 21 normal and not one affected female. This gives $X^2 = 7.00$, which corresponds for 1 d.f. to $P<0.01$. So we feel justified to consider the deafness in these families to be due to a sex-linked recessive gene.

Neither *Sataloff* nor *Parker* mention associated features except that in Parker's family two of the deaf members were of a low grade intelligence. In this connection it is interesting to note that the three deaf members of the De B. family were also of a low intelligence, while all the other members were of normal intelligence.

In the family De B. the hearing loss was as severe as in the cases described by the other authors: it was more than 70 db. for all frequencies up to 8000 cycles. But the dip at 1000 cycles and at 4000 cycles, observed by *Parker* in nine of his thirteen cases, did not occur in our family. Obviously we do not yet possess enough information about hearing in cases with this type of deafness to allow us to speak of a characteristic audiometric pattern. The fact, however, that in most cases some hearing is present up to 8000 cycles seems interesting as in most cases of other types of recessive congenital deafness, the hearing loss is apparently complete for the frequencies above 1000 cycles.

Summary

Two families, one discovered in the literature and one personal observation, are described. The fact that in both families the cases of congenital deafness occur in three consecutive generations, that all were of the male

sex, that each time the gene was transmitted by a healthy female who has at least one deaf brother and, finally, that the sex ratio is not compatible with the expectation in autosomal recessive inheritance, led us to assume that in both families the deafness was caused by a sex-linked recessive gene.

Zusammenfassung

Beschreibung von Fällen angeborener Taubheit in zwei Familien aus der Literatur und auf Grund persönlicher Beobachtung. Da bei beiden Familien die Fälle angeborener Taubheit in drei aufeinanderfolgenden Generationen und nur beim männlichen Geschlecht auftreten, da jedesmal das Gen durch eine gesunde Frau übertragen wurde, die wenigstens einen tauben Bruder hatte, und das Geschlechtsverhältnis nicht den Erwartungen bei autosomaler rezessiver Vererbung entsprach, wird angenommen, dass die Taubheit in beiden Familien durch ein geschlechtsgebundenes rezessives Gen verursacht wurde.

Résumé

L'auteur rapporte deux arbres généalogiques dont un de la littérature dans lesquels une surdité congénitale se rencontre dans trois générations consécutives. Vu que tous les atteints sont du sexe mâle et que l'affection est transmise par des femmes atteintes qui ont au moins un frère sourd, et que le «sex ratio» ne peut pas être expliqué par une hérédité autosomale récessive, il est justifié de considérer la transmission héréditaire en rapport avec un gène récessif localisé dans le chromosome X.

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ON THE GENETICS OF THE HAPTOGLOBINS

By F. GALATIUS-JENSEN

Since the last publication (4) our study material has increased so considerably that a follow-up of earlier presented figures appears justified.

In the meantime, *Fleischer* and *Lundevall* (3) have presented a fairly comprehensive genetic study of the haptoglobins, which is in conformity with the Danish findings. To the author's knowledge, other genetic studies have not been published during the past year, but preliminary investigations of the differences in the Hp gene frequencies between Africans and Caucasians have been published by *Sutton, Neel, Binson* and *Zuelzer* (14) and later by *Allison, Blumberg* and *ap Rees* (1). A Finnish study (8) is on the way, so far with results fully consistent with the genetical hypothesis advanced by *Smithies* and *Walker* (13). In May 1958 it comprised 43 families with 104 children and 84 mother-child combinations.

Technique

The technique was discussed at some length earlier (4). Only a few supplementary remarks shall be submitted here.

Samples of potato starch supplied by several starch factories in various parts of Denmark were tried for the preparation of the gel. No starch sample was encountered which could not be easily adjusted to a suitable degree of hydrolysis. The necessary amount of hydrochloric acid varied somewhat from sample to sample. The method described earlier (4) to determine the correct amount of hydrochloric acid for the hydrolysis of a starch sample has proved unsatisfactory and was abandoned.

To be able to give easily reproducible directions it was tried to simplify the previously described preparation of the hydrolyzed starch. The procedure is as follows: Hydrolysis now takes place at 37 centigrades, an incubator with this temperature being available in most laboratories.

Utensils and flasks are preheated to 37 degrees. The amount of starch to be hydrolyzed is placed in one flask and the necessary amounts of hydrochloric acid and acetone are mixed in another flask, whereupon the two flasks are left in the incubator until the following day. The contents of the two flasks are then mixed, and with the preheating described the hydrolysis should be stopped after about 15 minutes. The remaining procedure is as earlier described.

The influence of time, temperature and amount of hydrochloric acid on the degree of hydrolysis was studied. With a hydrolysis time of between 10 and 20 minutes a usable starch was obtained. When the time of hydrolysis was 10 minutes the gel was rather viscous; at 20 minutes it was somewhat looser. It was tried to change the temperature from 35 to 40 degrees. Within these limits, no appreciable change in the consistency of the gel was observed. With time and temperature being kept constant at 15 minutes and 37 centigrades, the rate of variation in amount of hydrochloric acid consistent with optimal hydrolysis of the starch was studied. It will appear from Table 1 that in one sample of starch the amount of 12 n hydrochloric acid could be varied from 2.55 to 2.25 ml. per 100 gms. of starch without any noticeable change in the consistency of the resulting gel.

Especially for the diagnosis of type Hp 1-1 it is essential that the position of the free haemoglobin be completely clear of the haemoglobin-haptoglobin and of the beta-globulin. If the pH of the buffer solution used for the preparation of the gel was kept at about 9.5 (an approximation is obtainable with 0.0075 mol. of boric acid and 0.006 mol. of sodium hydroxide), the free haemoglobin was found to lie a few mm. to the right of the beta-globulin.

Table 1

The relation between the quality of the hydrolyzed starch and the amount of hydrochloric acid used for the hydrolysis

ml of 12 n hydrochloric acid per 100 gms of starch	quality of starch
2.90	too loose
2.55 2.40 2.25	optimal consistency
2.06	viscous, but usable
1.83	too viscous

The technique developed by *Poulik* (12) using a discontinuous system of buffer solutions (Tri citrate for the starch gel and boric acid – sodium hydroxide for the bridge compartments) was tried. This method was found to represent no definite advantage when staining with Amidoblack was employed. When, on the other hand, a benzidine solution was used for staining, the Hp patterns of sera to which haemoglobin had been added in the usual amounts (300 mg.%) appeared to stand out markedly better in a gel prepared with "Tris" than in the usually employed gel prepared with boric acid – sodium hydroxide. Using this method it was possible repeatedly to determine the Hp group of children whose Hp pattern, using the gel made with boric acid – sodium hydroxide, was too faint to be discernible by Amidoblack staining or even by the more sensitive benzidine staining.

Results

The present study included 2046 unrelated, healthy persons, 205 families, 1037 mother-child combinations and 207 pairs of twins. In addition, the Hp groups of 250 diseased persons were examined. These figures include the following, earlier published figures (4): 1033 unrelated adults, 100 families with 278 children, 593 mother-child combinations and 101 pairs of twins.

Comprehensive blood grouping was done on nearly all persons in the study apart from the pathological blood specimens on which, in most instances, the examination was restricted to determination of the Hp group. On all blood samples, blood grouping comprising the A_1A_2BO, MN, P and Rh (C, D, E, c) systems was done. On the members of the families, the twins and the persons from the paternity cases included in this study, further blood grouping according to the S, K, Fy(a) and Le(a) systems was performed. On most of the members of the 87 families and the 187 pairs of twins, sera from whom were supplied by Dr. M. Hauge, blood grouping according to the Lu(a) system was also done. On 119 pairs of twins and on the members of 181 families an additional Gm grouping was done. The blood grouping of the 87 families and the 187 pairs of twins was performed by *Hauge*. All other blood grouping was done at the University Institute of Forensic Medicine. The Gm grouping was done by Dr. *P. Linnet-Jepsen*, Aarhus; the results were published recently (7). In an appendix a list was given of the blood groups, Gm and Hp groups of 195 families. The blood groups of the remaining 10 families are recorded in an appendix to this article.

The results of the Hp grouping in unrelated individuals, tabulated according to sex, are given in Table 2. The difference between males and females was clearly insignificant. The pooled number of males and females was therefore used in the calculation of the gene frequencies.

Table 2

Distribution of the Hp groups in 2046 unrelated individuals

	Males			Females			Total Males and Females	
	obs.	exp.	χ^2	obs.	exp.	χ^2	number	percent
Hp 1-1	83	97.3	2.1016	245	230.7	0.8864	328	16.03
Hp 2-2	235	222.8	0.6680	516	528.2	0.2818	751	36.71
Hp 2-1	289	286.9	0.0154	678	680.1	0.0065	967	47.26
Total	607	607.0	2.7850	1439	1439.0	1.1747	2046	100.00

$$\chi^2 = 3.9597 \text{ (for 2 d.f., P} = 0.2-0.1)$$

The gene frequencies were calculated in the manner usually employed in the case of a two allele system:

$$Hp^1 = \frac{2 \times 328 + 2 \times \frac{967}{2}}{2 \times 2046} = 0.397$$

$$Hp^2 = \frac{2 \times 751 + 2 \times \frac{967}{2}}{2 \times 2046} = 0.603$$

The gene frequencies differed slightly from the figures earlier published (Hp^1:0.403; Hp^2:0.597). Among 1.000 Norwegians, *Fleischer* and *Lundevall* (3) found Hp^1:0.363 and Hp^2:0.637.

The genotype frequencies were:

$$Hp^1/Hp^1: 0.397^2 = \qquad 0.1576$$
$$Hp^2/Hp^2: 0.603^2 = \qquad 0.3636$$
$$Hp^2/Hp^1: 0.397 \times 0.603 \times 2 = \quad 0.4788$$
$$\overline{\qquad\qquad\qquad 1.0000}$$

The relationship between the frequencies observed and expected will appear from Table 3. The differences were insignificant.

These calculations were based upon the two allele hypothesis. From a succeeding paper in this issue it will appear that a third, probably rare, Hp allele might exist.

The Hp groups appear to be independent of the blood groups indicated in Table 4. Using the chi square method, all P-values were found to be higher than 0.05 and equally distributed on either side of P = 0.50.

Table 3

Observed and expected frequencies of the Hp groups

	obs.	exp.	χ^2
Hp 1-1	328	322.5	0.0938
Hp 2-2	751	743.9	0.0678
Hp 2-1	967	979.6	0.1621
Total	2046	2046.0	0.3237 (for 1 d.f., P = 0.7–0.5)

Table 4

Hp groups in relation to blood groups and Gm groups

	A_1	A_2	0	B	A_1B	A_2B	M	N	MN	S	s
Hp 1-1	91	31	139	39	5	5	92	64	148	117	124
Hp 2-2	246	65	305	78	19	14	208	143	376	329	288
Hp 2-1	295	103	408	98	27	18	298	193	450	399	393

	R_1r	R_2R_2	R_2r	rr	R_1R_1	R_1R_2	R_0r	R r	$R''r$	R_1Rz
Hp 1-1	98	7	47	49	47	52	4	0	0	0
Hp 2-2	243	14	98	119	122	111	11	3	3	1
Hp 2-1	318	26	121	134	195	134	8	6	1	0

	P+	P—	Le(a+)	Le(a—)	K+	K—	Fy(a+)	Fy(a—)
Hp 1-1	240	65	26	100	13	292	84	46
Hp 2-2	550	170	56	279	43	677	209	132
Hp 2-1	732	207	83	353	61	874	292	160

	Lu(a+)	Lu(a—)	Gm(a+)	Gm(a—)
Hp 1-1	1	30	43	43
Hp 2-2	11	78	119	92
Hp 2-1	10	112	158	117

Families

The composition of the family material appears from Table 5. A good over-all agreement is found between the observed and expected number of the various parental combinations. Among the children no significant difference is found between observed and expected, but a tendency to an increased number of heterozygous children in the matings Hp 2-1/Hp 2-2 and Hp 2-1/Hp 1-1 is apparent from the table.

Table 5

Hp groups of family material

| group | Parents | | | Children | | | | | | | | | |
| | number | | | Hp 1-1 | | Hp 2-1 | | Hp 2-2 | | | | | |
	obs.	exp.	χ^2	obs.	exp.	obs.	exp.	obs.	exp.	χ^2	d.f.	undev.	Total
Hp 1-1+Hp 1-1	5	5.1	0.0020	9	9.0	0	0	0	0	–	–	0	9
Hp 1-1+Hp 2-1	33	30.9	0.1427	36	42.5	49	42.5	0	0	1.9882	1	0	85
Hp 1-1+Hp 2-2	18	23.5	1.2872	0	0	42	42.0	0	0	–	–	0	42
Hp 2-1+Hp 2-2	72	71.4	0.0050	0	0	104	92.5	81	92.5	2.8594	1	7	192
Hp 2-2+Hp 2-2	26	27.1	0.0446	0	0	0	0	63	63.0	–	–	5	68
Hp 2-1+Hp 2-1	51	47.0	0.3404	26	27.75	57	55.5	28	27.75	0.1532	2	2	113
Total	205	205.0	1.8219	71		252		172		5.0008	4	14	509
	(for 5 d.f., P = 0.9–0.8)					(for 4 d.f., P = 0.3–0.2)							

In order to investigate this tendency further a summation of Canadian (13), Norwegian (3) and Finnish (8) materials was made. Parents of the combinations Hp 2-2 Hp 1-1 had 52 children of type Hp 1-1 and 48 children of type Hp 2-1; these figures are obviously very close to expectation. On the other hand, parents of the mating type Hp 2-1/Hp 2-2 had a total of 157 children of type Hp 2-1 and 127 children of type Hp 2-2, which shows a tendency in the same direction as mentioned above. The combined results show a significant increase in the number of heterozygous children from the mating type Hp 2-1/Hp 2-2 and a corresponding significant shortage of children of type Hp 2-2.

This tendency could probably – at least partially – be explained by a later development of Hp 2-2, with the result that a bigger proportion of this genotype occurs among the undeveloped. It appears from the table that children with undeveloped Hp groups were found only in instances where they either must or at least could be Hp 2-2. The theory of Hp 2-2 being developed later than the two other types is supported by the following

observations: In a study of healthy adults, *Nyman* (9) found that persons belonging to the Hp 2-2 group had a smaller average concentration of haptoglobin than the two other types, Hp 1-1 and Hp 2-1. Presuming that the difference of the haptoglobin concentration in the sera of the three types are the same in the first months of life as they are later, it might reasonably be expected that a person of type Hp 2-2 is determinable later than an Hp 1-1 or an Hp 2-1. In keeping with this, the number in the age group 1–4 months of individuals belonging to the Hp 2-2 group was smaller than expected, while the number of Hp 1-1 was above expected values (Table 6).

Table 6

Distribution of Hp groups among children between 1 and 4 months

	obs.	exp.	χ^2	percent
Hp 1-1	57	48.7	1.4146	18.44
Hp 2-2	104	112.4	0.6278	33.66
Hp 2-1	148	147.9	0.0001	47.90
Total	309	309.0	2.0425	100.00
			(for 2 d.f., P = 0.5–0.3)	

Expected numbers are calculated from frequencies given in table 2

Table 7

Hp grouping only possible by staining with benzidine (1 month to 18 years)

	obs.	exp.	χ^2
Hp 1-1	18	11.5	3.6739
Hp 2-2	43	26.5	10.2736
Hp 2-1	12	35.0	15.1143
Total	73	73.0	29.0618 (for 2 d.f., P<0.001)

The patterns of 73 out of 1244 examined children aged between 1 month and 18 years were determinable only with benzidine staining. Table 7 shows the distribution.

That the type Hp 1-1, which had the highest average amount of hapto-globin, was represented by a number higher than expected in sera whose

Hp pattern was determinable only with benzidine, may seem strange at first sight, since this staining method is undoubtedly more sensitive than staining with Amidoblack. However, the explanation appears to be that the benzidine staining offers a better differentiation between the Hp 1-1 and the pattern in which the haptoglobin is still missing, because in Amidoblack staining the haemoglobin-haptoglobin band in type Hp 1-1 may occasionally merge with the beta-globulin. The diagnosis is then obtained by the double line in the benzidine staining, one of the bands being haemoglobin-haptoglobin, the other free haemoglobin.

The phenomenon that a higher number than expected of type Hp 2-2 is detectable only by the more sensitive staining may be explained by the fact that this type, as mentioned previously, has the smallest average concentration of haptoglobin, with the result that later than the two other types it reaches the threshold value above which the patterns are demonstrable not only in benzidine staining but even in Amidoblack staining.

Table 8

Distribution of Hp groups among 132 mothers to children with undeveloped Hp-pattern

	obs.	exp.	χ^2
Hp 1-1	16	22.8	2.0281
Hp 2-2	55	46.2	1.6762
Hp 2-1	61	63.0	0.0635
Total	132	132.0	3.7678 (for 1 d.f., $P = 0.1–0.05$)

A comparison of the number of Hp 2-1 + Hp 1-1 and the number of Hp 2-2 determinable only with benzidine showed a ratio of 14:9 in the age group 1–2 months and 7:13 in the age group 2–4 months. Consequently, benzidine staining seems to be most necessary for the demonstration of Hp 2-1 + Hp 1-1 in the age group 1–2 months and most essential for the demonstration of Hp 2-2 in the age group 2–4 months.

Further evidence in support of this theory was afforded by the distribution of the 132 mothers of children with undeveloped Hp patterns found in the mother-child combinations recorded in Table 9. It will appear from Table 8 that the number of Hp 2-1 mothers corresponded to the number expected, while the number of Hp 1-1 was smaller and the number of Hp 2-2 higher than expected.

16

<div align="center">

Table 9

Hp groups of 1035 mother-child combinations

</div>

Mother				Child					
	Number				Number				
Type	obs.	exp.	χ^2	Type	obs.	exp.	χ^2	d.f.	
				Hp 2-1	100	98.3	0.0294		
Hp 1-1	179	163.1	1.5500	Hp 1-1	63	64.7	0.0447		
				Total	163	163.0	0.0741	1	(P = 0.8–0.7)
				Undev.	16				
				Hp 2-1	119	121.9	0.0690		
Hp 2-2	362	376.3	0.5434	Hp 2-2	188	185.1	0.0454		
				Total	307	307.0	0.1144	1	(P = 0.8–0.7)
				Undev.	55				
				Hp 2-1	232	216.5	1.1010		
Hp 2-1	494	495.6	0.0052	Hp 2-2	119	130.5	1.0134		
				Hp 1-1	82	86.0	0.1860		
				Total	433	433.0	2.3004	2	(P = 0.5–0.3)
				Undev.	61				
Total	1035	1035.0	2.0986 (for 2 d.f., P = 0.5–0.3)	Total	1035	1035.0	2.4889	4	(P = 0.7–0.5)

Mother-Child Combinations

The Hp groups of 1037 mother-child combinations were determined. Two combinations, where the mothers had ahaptoglobinaemia, were omitted from the table. The two mothers are dealt with in a separate paper. There was good agreement between the observed and the expected numbers of mothers. Good agreement was likewise found between the observed and the expected numbers of children. The expected distribution of the children was calculated on the basis of the difference between the total number of cases and the number of undeveloped cases, as the latter group might not be evenly distributed over the three Hp types. The numerical distribution of the children of the Hp 2-1 mothers was not quite in agreement with the expected figures. As in the family material, the Hp 2-1 mothers had more heterozygous than homozygous children. Here as in the family study the difference, which was not significant, may be due to a

lagging behind of the number of Hp 2-2 ($\chi^2 = \dfrac{15.5^2}{216.5} \times 2 = 1.097$, P for 1 d.f. $= 0.3-0.2$).

Twins

Altogether 207 pairs of twins were examined. Of these, 206 pairs are included in the table. The pair omitted (heterozygous twins born in 1946) appeared at two examinations performed at an interval of about 6 months to have no haptoglobin. They belong to family H 13 (7).

One of a pair of heterozygous twins aged 65 showed ahaptoglobinaemia at the first examination. A repeated examination performed some months later while the man was in hospital with urine retention complicated by epididymitis showed a normal Hp 2-2 pattern. Special reference to this case is made in the following paper.

36 of the 126 pairs of presumably monozygous twins were monochorial. The sera originated from a re-examination of E. Essen-Møller's material of Swedish twins (2). The remaining 90 pairs had identical blood groups and appeared on polysymptomatic similarity test to be most likely monozygous.

Two pairs with identical blood groups, but rather different in appearance and stature had different Hp groups. By a peculiar coincidence the same two pairs differed also in Gm groups.

Table 10

Hp groups of 206 pairs of twins

	Hp groups identical	Total	Hp groups different	Total	Total
Presumably monozygous twins*	Hp 1-1:19 Hp 2-2:50 Hp 2-1:57	126	Hp 1-1/Hp 2-2:0 Hp 2-2/Hp 2-1:0 Hp 2-1/Hp 1-1:0	0	126
Dizygous twins	Hp 1-1: 6 Hp 2-2:23 Hp 2-1:21	50	Hp 1-1/Hp 2-2: 2 Hp 2-2/Hp 2-1:18** Hp 2-1/Hp 1-1:10	30	80
Total		176		30	206

* e.i. of identical sex, blood groups, Hp groups and of high concordance in the similarity test, 36 pairs were monochorial.
** Two pairs in this group had identical sex and blood type. They were, however, markedly different in stature and appearance, in addition they showed different Gm groups.

Hp Grouping of Pathological Sera

Nyman, Gydell and *Nosslin* have published studies of the haptoglobin under pathological conditions (10). On examination of the sera with the starch gel technique normal patterns – except for variations in strength going as far as the complete ahaptoglobinaemia – were always found (11).

In the present study, the Hp groups of approximately 250 pathological sera from persons with a large variety of diseases were examined. A brief account of this investigation was given earlier (4). As expected, examples of ahaptoglobinaemia were found among patients with haemolytic disease, liver cirrhosis and hepatitis. These findings confirm the observations reported by French and Swedish investigators (6. 10). Examples of ahaptoglobinaemia were found also in one case of uraemia and in one case of Addison's disease. The primary aim of the present study was, however, to examine whether Hp patterns, different from the usual ones, turned up among the pathological sera, many of which showed disturbances in the alpha 2 globulin content. That was never the case. In many instances the patterns were more intense and in some instances weaker than those normally observed, but the position and the relative intensity of staining of the different bands were always the same. In diseases causing tissue destruction and repair the Hp patterns showed more intense staining than usual. Some of these sera were found to have a haptoglobin content of 6–8 times the normal amount.

A gross quantitative estimate of the haptoglobin content of a serum is obtainable by electrophoresis of aliquots of the serum to which increasing amounts of haemoglobin have been added. All haptoglobin is considered to be bound to the haemoglobin when free haemoglobin appears as a separate, illdefined zone which, in the experiments here reported, was lying near the position of the beta-globulin. The appearance of the free haemoglobin is seen most clearly after staining with benzidine.

The Use of the Hp Groups in Cases of Disputed Paternity

On account of the favourable distribution of the gene frequencies the theoretical exclusion rate of the Hp system is rather high, viz. 0.1821. The Hp system is therefore a welcome supplement to the blood grouping systems already used in cases of disputed paternity.

Table 11 shows a survey of 88 cases involving a total of 178 men. In 74 cases only two men were included. If one of these were the father, an exclusion rate of about half the theoretical one should be obtained. 13 out

Table 11

88 cases of disputed paternity

| | | Number of putative fathers | | | |
		1	2	3	4
Number of	0	6	61	4	2
excluded men	1	1	13	1	0

Figures in cells indicate number of paternity cases

of 148 men could be excluded. This gave an exclusion rate of 8.78 per cent., a figure very near to the 9.1 per cent. which should be obtained on the assumption mentioned above.

It is the opinion of the University Institute of Forensic Medicine, Copenhagen, that the Hp system has now been examined so extensively that it may be used, with certain reservations, in forensic medicine. In December 1957 the Danish Medico-Legal Council made the following statement concerning the use of the Hp system:

> "The Medico-Legal Council finds that, provided the technique is impeccable and the haptoglobin patterns well developed so as to permit clear and unambiguous differentiation, the weight attachable to exclusion of paternity based on the inheritance of the haptoglobins and demonstrated by electrophoresis in a starch gel medium must, at the present scientific stage, be considered of about the same magnitude as the weight attachable to exclusion according to the Rh, P or K systems, i.e. between 99 and 99.9 per cent.
>
> This evaluation should, however, be taken with a certain reservation in cases where one or more of the parties to a paternity case are not in good health at the time of withdrawal of the blood sample."

Summary

A report is given of the determination of the Hp groups of 2046 unrelated, healthy individuals, 205 families with 509 children, 1037 mother-child combinations and 207 pairs of twins. The results provide further support of the genetic theory advanced by *Smithies* and *Walker*.

The results of Hp grouping of some 250 pathological sera are reported. Apart from cases of ahaptoglobinaemia, which were encountered especially in the presence of haemolytic disease, the Hp groups were always easily determinable.

A survey of 88 cases of disputed paternity showed good agreement between observed and expected exclusion rates.

The Hp system is now used at the University Institute of Forensic Medicine, Copenhagen, in selected cases of disputed paternity. As the theoretical exclusion rate is rather high (0.1821), the Hp system offers a good supplement to the blood grouping systems in use. Exclusion according to the Hp system may now be considered almost equally as important as exclusion according to the Rh, P or K systems.

Zusammenfassung

Es wird über die Bestimmung der Haptoglobin-Gruppen von 2036 nicht verwandten, gesunden Personen, 205 Familien mit 509 Kindern, 1037 Mutter-Kind-Kombinationen und 207 Zwillingspaaren berichtet. Die Ergebnisse unterstützen weiterhin die genetische Hypothese von *Smithies* und *Walker*.

Die Ergebnisse der Hp-Bestimmung bei 250 pathologischen Sera werden mitgeteilt. Abgesehen von Fällen von Ahaptoglobinämie, die sich besonders bei hämolytischer Erkrankung finden, waren die Hp-Gruppen immer leicht zu bestimmen. Ein Überblick über 88 Fälle von umstrittener Vaterschaft zeigte eine gute Übereinstimmung zwischen erwarteter und gefundener Ausschlußrate.

Das Hp-System wird jetzt im Univ.-Institut für gerichtliche Medizin, Kopenhagen, bei ausgewählten Fällen umstrittener Vaterschaft verwendet. Da der theoretische Ausschlußwert ziemlich hoch ist (0.1821), stellt das Hp-System eine gute Ergänzung zu den gebräuchlichen Blutgruppen-Systemen dar. Der Vaterschaftsausschluß durch das Hp-System kann jetzt als fast genau so wichtig angesehen werden wie der Ausschluß durch das Rh-, P- und K-System.

Résumé

L'examen des groupes Hp chez 2036 individus normaux non apparentés, de 205 familles avec 509 enfants, de 1037 mères et enfants et de 207

paires de jumeaux a permis de confirmer la théorie génétique de *Smithies* et *Walker*.

En plus, le groupe Hp a été déterminé dans 250 cas pathologiques. A part les cas d'ahaptoglobinémie qui ont surtout été rencontrés dans la maladie hémolitique, il a été toujours facile de mettre en évidence les groupes Hp. Dans 88 cas de recherche en paternité, il y avait une bonne concordance entre les probabilités théoriques et observées d'exclusion.

L'institut universitaire de médecine légale à Copenhague se sert maintenant du système Hp dans des cas spéciaux de recherche en paternité. Etant donné que la probabilité de l'exclusion est plutôt haute (0,1821), le système Hp est un supplément appréciable des groupes sanguins ordinaires. L'exclusion par le système Hp peut être considérée aujourd'hui comme tout aussi importante que celle due aux groupes Rh, P ou Ke.

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APPENDIX

Supplementary list of families

Key to appendix: cf. Acta genet. *8:* 179 (1958)

No.	Sex	Y. of b.	AB0	MNS	Rh	P	Le(a)	K	Fy(a)	Hp
G 109	M	1919	A_1	N	R_1r	+		—		2-2
	F	1929	0	MN	R_1R_1	+		—		2-2
	F	1957	A_1	N	R_1r	+		—		2-2
	M	1957	A_1	MN	R_1R_1	+		—		2-2
G 110	M	1925	0	Ms	R_1R_1	+		—		2-2
	F	1931	0	MNS	R_2r	—		—		2-2
	M	1957	0	MNS	R_1R_2	—		—		2-2
	F	1957	0	MS	R_1r	—		—		2-2
G 111	M	1892	A_1	MNS	R_1r	—	—	—	+	2-2
	F	1891	A_1	MS	R_1r	—	—	—	—	2-1
	M	1918	0	MS	R_1r	—	—	—	+	2-1
HB 1	M	1915	A_1	MNs	R_2r	+	—	—	+	2-1
	F	1919	A_1	MS	R_2R_2	+	+	—	+	2-2
	M	1945	A_1	MNS	R_2r	+	—	—	—	u.
	M	1946	0	MNS	R_2r	+	—	—	—	2-1
	F	1955	A_1	MNs	R_2r	+	+	—	+	u.
HB 2	M	1927	0	Ns	R_2R_2	+	—	—	+	2-2
	F	1928	A_1	Ns	R_1r	—	+	+	+	2-1
	M	1954	A_1	Ns	R_2r	+	+	—	+	2-1
	F	1956	A_2	Ns	R_2r	+	+	—	+	2-1

No.	Sex	Y .of b.	AB0	MNS	Rh	P	Le(a)	K	Fy(a)	Hp
HB 3	M	1914	A_2B	MNS	R_1r	—	—	—	+	1-1
	F	1920	B	Ms	R_1R_2	+	—	—	+	2-1
	M	1945	B	MS	R_1r	+	—	—	+	2-1
	F	1948	A_2	MNs	R_2r	—	—	—	+	1-1
HB 4	M	1914	0	Ms	rr	—	—	+	—	2-1
	F	1918	A_1	Ms	R_2r	—	—	—	+	2-1
	M	1941	0	Ms	R_2r	—	—	—	—	2-1
	M	1944	0	Ms	rr	—	—	+	—	1-1
	F	1950	0	Ms	rr	—	—	+	—	2-1
	M	1953	0	Ms	R_2r	—	—	+	+	1-1
HB 5	M	1909	0	MS	rr	+	—	—	—	2-2
	F	1908	A_2	Ns	R_1R_2	+	—	—	—	2-2
	M	1945	A_2	MNs	R_2r	+	—	—	—	2-2
	M	1948	A_2	MNs	R_1r	+	+	—	—	u.
	F	1949	A_2	MNs	R_1r	+	—	—	—	2-2
HB 6	M	1900	A_2	MS	R_1R_2	—	—	—	—	2-1
	F	1917	A_1	MNs	R_1r	+	—	—	+	2-1
	F	1944	A_1	MS	R_1r	+	—	—	+	1-1
	F	1950	0	MS	R_1R_1	—	—	—	+	1-1
HB 7	M	1911	0	MNS	R_1r	+	—	—	+	2-1
	F	1919	A_2	MNs	R_1R_2	+	+	—	+	2-1
	F	1943	A_2	MNs	R_1r	+	—	—	+	1-1
	F	1944	0	Ms	R_1R_2	+	—	—	+	2-1
	M	1951	A_2	NS	R_1r	+	—	—	+	u.

From the University Institute of Forensic Medicine, Copenhagen

RARE PHENOTYPES IN THE Hp SYSTEM

By F. GALATIUS-JENSEN

By electrophoresis of several thousands of sera from healthy persons, two Hp phenotypes different from those described by *Smithies* (14) were encountered. One had an apparently total lack of haptoglobin, the other, which was found on two occasions only, had a well–defined haptoglobin pattern, but differed from the three types earlier described.

Examples of lack of haptoglobin – ahaptoglobinaemia – have been reported in connection with haemolytic disease and in the presence of hepatitis and liver cirrhosis (5, 6, 11, 12, 13), where increased haemolysis was demonstrated by means of Cr 51 tagged erythrocytes (4, 7, 12).

Allison, Blumberg and *ap Rees* (1) found a high proportion of ahaptoglobinaemia among Nigerians (in 32 out of 99). Nothing was stated about possible haemolytic disease in the persons examined.

As earlier reported (2), sera from newborn infants rarely show an Hp pattern. Our present experience of the development of haptoglobin in relation to age can be summarized as follows: A few children (in the present study between 5 and 10 percent) have a more or less distinct Hp pattern at birth. – In sera from 10 dead, prematurely born infants a distinct Hp 2-2 pattern was found in one instance in an infant weighing only 1000 gms. – On examination of capillary blood 8 days after birth, 8 of the 10 infants with determinable type in the cord blood showed patterns identical with those first determined, while 2 had no haptoglobin. A reasonable explanation of the disappearance of the haptoglobin seems to be that the amount of haptoglobin available at the time of birth in the serum of these two infants was bound to free haemoglobin from disintegrating blood corpuscles and removed from the blood. This would agree with the findings of *Laurell* and *Nyman* that haptoglobin disappears in patients with untreated pernicious anaemia (11) or following injection of haemoglobin into healthy persons (8). – The haptoglobin found in the cord bloods might have passed

transplacentally from mother to child, as was the case with the gamma-globulin found by *Grubb* (3, 9). To examine this possibility the Hp groups of the mothers were determined. If the infants with developed Hp type at birth had their haptoglobin from their mothers, they would naturally have an Hp type identical with that of the mother. In half of the cases, however, the Hp types of the infants differed from the mother's type.

The percentage of determinable Hp patterns rises rapidly during the first weeks and months of life. – After one week the Hp group of more than 40 percent can be determined, after 2 months the determinable percentage is between 80 and 90, and in infants over 4 months old a missing Hp pattern is a rarity. However, between 1 and 2 percent (12 out of 745) of the examined sera from children aged between 4 months and 15 years showed ahaptoglobinaemia.

Even among apparently healthy adults the present study revealed a few examples of sera showing no detectable trace of haptoglobin. In view of the fact that ahaptoglobinaemia among apparently healthy adults is found only exceptionally in the Danish population, it was thought useful to consider these findings in somewhat greater detail.

In 205 families no example of ahaptoglobinaemia among the adults was encountered. – Among 207 pairs of twins, one man, aged 65, showed no trace of haptoglobin patterns at the first examination. He had one son, whose serum showed a completely normal Hp 2-1 pattern. At the time of examination the father was apparently in good health. One month later he was hospitalized with urine retention on account of a benign hypertrophy of the prostate. While in hospital he developed epididymitis, in connection with which the sedimentation rate rose to above 100 mm per hour. A new blood sample withdrawn at that time showed a normal Hp 2-2 pattern. This finding is in good agreement with the numerous reports, especially by French workers, of the rise in the haptoglobin level of the blood following infection, the rise being stated to be more or less proportional to the increase of the sedimentation rate. On repeated examination three months later the Hp 2-2 pattern was unchanged. – In addition one pair of heterozygous twins born in 1946 and belonging to family H 13 (10) showed ahaptoglobinaemia by repeated examination with an interval of six months.

Among 1037 mother-child combinations, two mothers showed ahaptoglobinaemia. It was endeavoured to obtain new blood samples. In one of the cases the efforts were fruitless, however, as the woman flatly refused. In the other case a new blood sample withdrawn about one year after the first one showed a rather faint, but clearly discernible and completely
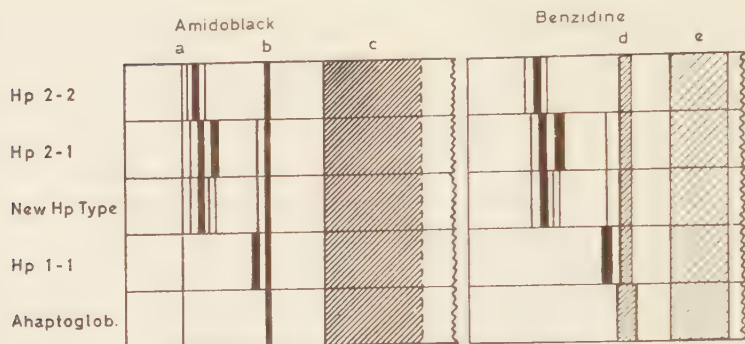
Diagram of Hp phenotypes

a: S-alfa$_2$ b: betaglobulin c: albumin d: free haemoglobin e: methaemalbumin
The Hp-patterns are situated between S-alfa$_2$ and betaglobulin. The free haemoglobin
is not indicated in Amidoblack staining.

normal Hp 2-2 pattern. Information of any disease at the time of the first withdrawal of blood could not be obtained with certainty, but she was found a few months later to have macrocytic anaemia. – Both children showed a normal Hp 2-1 pattern.

The fourth and last case of ahaptoglobinaemia found accidentally among the healthy adults examined, occurred in a man aged 32. He was apparently in good health, with no complaints. As he had a rather wide-spread family, an investigation of the Hp types of the family members was performed. The results appear from the pedigree.

It will be seen that 4 out of 6 brothers and sisters had ahaptoglobinaemia, one was a faint, but otherwise normal Hp 2-2, and one a perfectly normal Hp 2-1. In the next generation 4 had ahaptoglobinaemia, 2 had unusually weak patterns (i.e. just discernible in Amidoblack staining, easily discernible with benzidine), 3 were quite normal. The proband's mother had a weak, but normal Hp 2-2 pattern: his father was alive, but could not be persuaded to have a few drops of blood taken. – The proband was examined clinically by a haematologist using modern haematological techniques, including examination with Cr 51 tagged erythrocytes. Nothing abnormal was observed. A slight reduction of the 50 percent survival time, which was found to be 24 days (average 29 days), could not be considered significant.

The cause of the 4 cases of ahaptoglobinaemia described could not be established with certainty. The findings cannot, however, be explained by a third, silent allele, an Hp^0, in these cases occurring in a homozygous

form: Two of the four persons concerned were found at a later date to have a normal Hp 2-2 pattern. – The man aged 65 as well as the two women had offspring of type Hp 2-1 indicating the capability of the ahapto-globinaemic phenotype to convey an Hp^1 gene as well as an Hp^2 gene. In the family given in the pedigree there was no question either of a homo-zygous occurrence of a silent Hp gene. The wife of the propositus was Hp 2-1, which would appear to exclude the possibility of her child being Hp^0/Hp^0. If a silent gene, Hp^0, existed in the Danish population with even a low frequency, cases would show up among mother-child or father-child combi-nation of *mother (father)*: Type Hp^1/Hp^0 (simulating type Hp 1-1) and *child*: Type $Hp^2 Hp^0$ (simulating type Hp 2-2) – or vice versa. No example of this was found in more than 1000 mother-child combinations and in 205 families. – Only one of the four persons was subjected to thorough haematological examination. In that case the erythrocyte survival time seemed to be slightly reduced. – One of the women showed macrocytic
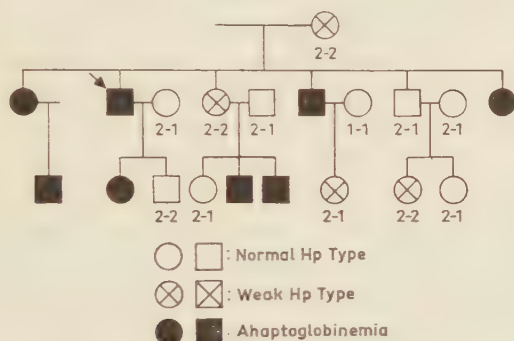
Pedigree I

Family with several examples of ahaptoglobinaemia

anaemia at a later date. These findings might indicate that in these two instances – or perhaps in all four instances – the ahaptoglobinaemia was caused by slight haemolytic disease, perhaps a slightly increased sequestra-tion rate of the blood corpuscles with a consequential surplus of haemo-globin in serum sufficient to bind the haptoglobin as soon as it is produced. – In one instance the ahaptoglobinaemia appeared to be hereditary. A pos-sible explanation is that a slight haemolytic disease from which the proband might suffer, was inherited in the family, and so indirectly caused the apparently hereditary ahaptoglobinaemia. – Another explanation, which at present cannot be ruled out, is that the production of haptoglobin was suppressed in some way or other, perhaps by some inhibitory gene. –
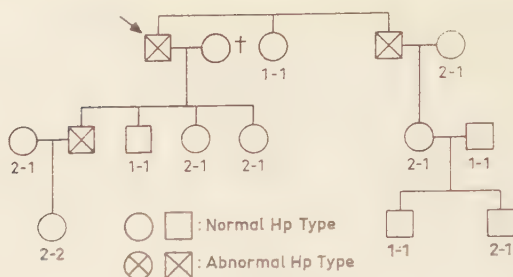
Pedigree II

Family with abnormal phenotype

Further investigations by modern haematological techniques of families showing examples of ahaptoglobinaemia among the adult members may elucidate this problem.

Apart from ahaptoglobinaemia, no Hp phenotype differing from the three types found by *Smithies* (14) has been described so far. Within the last few months a new phenotype was found on two occasions.

In a paternity case recently examined at the Institute of Forensic Medicine mother and child showed Hp groups, which at first sight were interpreted as Hp 2-2 and Hp 1-1 respectively. Careful study of the patterns revealed, however, that the mother was neither an Hp 2-2 nor a typical Hp 2-1. – The pattern was similar to that of an Hp 2-1 apart from one important difference: Instead of the strongest of the three bands near S alfa$_2$ in the position nearest to the anode, two much weaker, just discernible bands were found; one was lying at the normal position of the strongest of the three bands in Hp 2-1, the other just to the left of this location (i.e. at the position of the weakest and most anodically placed band in the Hp 2-2 pattern). As in Hp 2-1 – and in contrast to Hp 2-2 – a rather faint band of haptoglobin (at the position of the band in type Hp 1-1) was observed to the immediate left of the betaglobulin. Examination of another blood sample from the same person withdrawn a couple of weeks later showed an identical pattern, while the child showed a typical Hp 1-1 pattern as at the first examination. The female was 20 years old, apparently in good health. Delivery had taken place six months earlier and had been quite normal. Gynaecological examination after birth disclosed no evidence of disease. The serum was examined by free electrophoresis (Tiselius), paper electrophoresis and immuno-electrophoresis (Grabar & Williams). Nothing unusual was observed. – Family studies were not possible.

One month later during examination of blood from donors an example of an identical pattern was observed, this time in a man aged 60 in perfectly good health. As he had a rather widespread family, here was the chance of gaining some knowledge of the possible genetic background of the described phenotype. – The pedigree shows the extent of the family investigation.

Besides the proband two other members of the family – a brother and a son of the proband – showed the abnormal phenotype. One of the proband's sons appeared to be a normal Hp 1-1, and the son of the proband, who showed the abnormal phenotype, had a daughter, who was apparently a normal Hp 2-2.

It is not possible at present to offer a fully satisfactory interpretation of this phenotype. – One explanation may be that this new phenotype is an Hp 2-1, changed but slightly by the influence of some modifying gene. – Another possible explanation is the presence of a third Hp gene, either an unusually strong Hp^2 variant or an unusually weak Hp^1 variant. The new phenotype could then be explained as a heterozygote, where one of the two alleles represents the third Hp gene. A person of this type would, together with a normal Hp 2-1, be able to get the Hp types represented among the proband's children. – A third hypothesis is that a combination of this gene with either an Hp^1 gene or an Hp^2 gene results in the same phenotype. – That exogenous factors should be the cause of the phenotype seems less probable, as it appeared in three family members who for many years had been living apart under different conditions.

Whatever the explanation of this phenotype may be, it should be emphasized that it represents a possible source of error, as the abnormal Hp type may be easily mistaken for an Hp 2-2 (especially if Amidoblack staining is employed alone). This might give rise to erroneous exclusions in cases of disputed paternity. However, if only plain, clearcut Hp patterns are relied upon, this pitfall should be avoidable. The diagnosis Hp 2-2 can be considered as completely reliable only, when the rather weak band lying to the extreme right (nearest the anode) in the normal Hp 2-2 pattern is clearly visible, so that the examiner can be sure that only one band, not two bands, is lying here. If this band cannot be seen clearly, the diagnosis Hp 2-2 is probably correct, but the possibility cannot be ruled out that the pattern is another example of the phenotype described above. Staining with benzidine should always be included in the routine procedure.

Nothing definite can be said at present about the frequency of the phenotype described. A check of all our slabs stored in the Institute (more than 3000) revealed no example of this phenomenon. It is reemphasized,

however, that the decisive double line is difficult to see in slabs stained in Amidoblack, which are the only ones it has been possible to preserve. – In view of the fact that no example of apparent mother-child or father-child exclusions was encountered in over 1000 mother-child combinations and 205 families it appears justifiable to consider the described pheno-type as a rare exception, at any rate in the Danish population.

Summary

Cases of ahaptoglobinaemia among apparently healthy adults are des-cribed. In one case a family study was carried out, and a number of examples of ahaptoglobinaemia is discussed.

Examples are reported of a phenotype not previously described. A fa-mily study in which 3 examples of the phenotype were found, throwed some light on the genetic mechanism, but no definite conclusion can be drawn at present concerning the Hp components of the phenotype described. The importance of the phenotype as a possible source of error is emphasized.

Zusammenfassung

Fälle von Ahaptoglobinämie bei offenbar gesunden Erwachsenen wer-den beschrieben. In einem Falle wurde die Familie untersucht, und es fand sich dort eine Anzahl von Beispielen für Ahaptoglobinämie. Die Ursache der Ahaptoglobinämie wird diskutiert.

Von einem bisher noch nicht beschriebenen Phänotyp werden Beispiele mitgeteilt. Die Untersuchung einer Familie, in der drei Beispiele dieses Phänotyps gefunden wurden, warf einiges Licht auf die genetische Grund-lage, es können jedoch noch keine endgültigen Schlußfolgerungen gezogen werden, welche Hp-Komponenten bei diesem Phänotyp vorhanden sind. Seine Bedeutung als mögliche Fehlerquelle wird betont.

Résumé

Des cas d'ahaptoglobinémie chez des personnes adultes apparemment saines sont décrits. Dans un cas, l'examen de la famille a permis de dé-couvrir d'autres cas de cette affection.

Description d'un nouveau phénotype qui a été rencontré trois fois dans une même famille. Il permet de se faire une idée sur le mécanisme géné-

tique. Toutefois il n'est pas possible pour le moment de tirer des conclusions définitives concernant les facteurs Hp de ce phénotype. L'auteur attire l'attention sur le fait que ce phénotype peut induire en erreur.

ACKNOWLEDGEMENTS

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ON THE DIAGNOSIS OF ZYGOSITY IN TWINS AND THE VALUE OF BLOOD GROUPS

By NIELS JUEL-NIELSEN, ARNE NIELSEN
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The employment of the twin method in human genetics has frequently been the subject of criticism which has, as a rule, been well founded. It must be considered justifiable to undertake at intervals a methodological survey with the object of co-ordinating results and points of view from the various groups of twin research workers and to bring the twin method into agreement with the results which have been obtained in the intervening period by other research methods in human genetics.

The present paper will be limited first and foremost to treatment of the basic problem in every research concerning twins, viz. the *zygosity diagnosis* while the problems and sources of error otherwise associated with the employment of the twin method will be touched upon only indirectly.

The twin method is based upon the theoretical supposition that in the genetic sense two types of twins exist: monozygotic twins equipped with identical genes and dizygotic twins who in respect of heredity are as similar or as different as are siblings, on an average.

No direct cytological proof of the existence of these two different types of twins is available where man is concerned but both in general genetics and in human genetics comprehensive material has been obtained which supports the plausibility of the primary theory so uncontestably that the method must be regarded as being satisfactorily founded as a method of scientific research.

Theoretically, other possibilities may be presented regarding the origin of the phenomenon of twins, and this has in fact been done. However, clear evidence of the existence

of other types of twins is not yet available and, at present, it must be considered justified to ignore these types and particularly as their occurrence must be presumed to be rare and, therefore, without practical importance.

As regards the primary link in the working hypothesis mentioned above, viz, that in respect of genes, monozygotic twins are identically equipped this presumption, also, has been subjected to doubt by *Dahlberg* (1930), *Bouterwek* (1934) and *Newman, Freeman* and *Holzinger* (1937) among others. The above mentioned authors, although with slightly differing formulation, attribute conclusive significance to the so-called "asymmetry phenomenon" as a theoretically possible source of error in the twin method and thus for its basic foundation. *Bouterwek* was originally of the opinion that monozygotic twin partners differed in respect of their genetic endowment. In a later work (1934), however, he abandoned this hypothesis. *Dahlberg* expressed himself in an apparently paradoxical manner when at the same time as he employed the expression "genotypical asymmetries", he would not absolutely maintain that monozygotic twins differ genotypically. In a later work (1947) he maintains his points of view and draws comparison with the conditions in a single individual (as does *Bouterwek*) where the two halves of the body present what *Dahlberg* terms genetically determined differences despite the same hereditary endowment. *Newman* et al. interpreted the condition of asymmetry as "a third factor" which is independent in its relationship to the factors "heredity" and "environment" and in the opinion of these authors associated with the biological phenomenon of twinning.

In our opinion, the condition of asymmetry, the significance of which must still be considered to be unsolved, may with equal justification be regarded as a peristatically determined phenomenon and, in any case, it does not give any convincing ground to doubt the theory that monozygotic twins, as this expression is defined, are genotypically identical.

As regards the theoretical objections which have otherwise been raised against the twin method, it should only be mentioned that conclusive evidence is not yet available that the "primary biases" as summarized by *Price* (1950) have the thorough significance which it appears reasonable to attribute to them on theoretical considerations. However important these become in the employment of the twin method and the evaluation of the results obtained, they serve actually only to illustrate that the expression "environment" also includes the antenatal environment and that the information hitherto available concerning this subject is very limited and requires further elucidation. On the other hand, no justified doubt concerning the basic hypothesis of the twin method is raised.

Finally, it is worth emphasizing that a considerable proportion of the criticism which has been directed towards the twin research method concerns problems involved in the selection and treatment of material as was first pointed out by *Luxenburger* (1930). These requirements are relevant where every scientific investigation is concerned and are not directed particularly towards the twin method as such.

In twin investigations based upon numerically limited materials it is necessary that as exact zygosity diagnosis as possible be established concerning the actual individual pairs of twins. A satisfactory solution of this problem is of fundamental significance for the scientific employment of the twin method and, thus, for the possibilities of counteracting the other sources of error and "biases" which the twin method and also other scientific methods of investigation imply.

It should be pointed out historically, that the founder of research in-
vestigations in twins, *Galton*, possessed no criteria by which to differentiate
between monozygotic and dizygotic twins. He divided his twin material
into two groups: those who were identical at birth and throughout life
and those who differed at birth and in whom the difference became more
pronounced during development. It seems apparent that, by means of this
intuitive method, *Galton* attained a subdivision which corresponds quite
satisfactorily to the two types of twins.

By their investigations *Curtius* (1930). *Lassen* (1931) and *Steiner* (1935)
demonstrated that probably only a proportion of those twins who are re-
garded as monozygotic are monochoric. This does not, however, justify
the abandoning of examination of the afterbirth as an aid in the diagnosis
of zygosity. No case of certain dizygotic twin pairs (i.e. twins of different
sexes or blood groups) of proved monochoric origin has been published
so far. Consequently, it must be maintained that monochoria must be
regarded as the only existing proof of monozygosity and, therefore, that
monochoria is of decisive value in the twin method. The most important
drawback of this method is of a purely practical nature, viz. that only on
exceptional occasions is reliable and scientifically employable information
concerning the afterbirth available. This condition will always be a serious
handicap in the employment of the twin method unless obstetricians con-
ducting twin deliveries can be persuaded to examine and record compre-
hensive notes concerning the state of the afterbirth to a much greater
extent than previously.

It is quite obvious that a confirmed diagnosis of dichoria is of no value
as a proof of zygosity.

Siemens (1924) occupies an outstanding position in the attempts to ob-
tain a basis for a differentiation between the two types of twins. His poly-
symptomatic similarity test supplied for the first time a method which
could be employed practically but the theoretical basis failed in logical
respects. By systematizing the criteria which *Galton* employed intuitively
he attempted to counteract the practical difficulties in the employment of
the twin method. There can be no doubt whatsoever that, in this manner,
considerable progress was made but, on the other hand, it cannot be denied
that in this way one is frequently led into the vicious circle of argument so
fatal for the twin method of research: that monozygotic twins *are* mono-
zygotic because they are similar and that traits which occur concordantly
in monozygotic twins are hereditary while discordance is regarded *on
principle* as indicating that twins are not monozygotic.

The basis for *Siemens'* polysymptomatic similarity test remained un-

certain for a long period as no attempt or only a limited attempt was made to evaluate the extent of the criteria employed upon a twin material which was subdivided upon a confirmed basis. *Essen-Möller* (1941) was the first to attempt to illustrate these problems on a suitable and extensive material of twins. Commencing from the confirmed diagnostic criterion of monozygosity, monochoria, and the two confirmed diagnostic criteria of dizygosity, differences in sex and blood type, he was enabled to select a group of *definite monozygotic twins* and a group of *definite dizygotic twins*. From the results of the polysymptomatic similarity test employed upon these two groups, he obtained a basis for evaluation of the morphological criteria and the employment of these upon the remaining group who were neither monochoric nor differed as regards blood type. *Essen-Möller*'s work which appears to be little known in the Anglo-Saxon literature is also unique in other respects. The material was obtained during a long series of years in advance by means of a systematic investigation of the afterbirths in all twin deliveries in an obstetric departement. The twins were followed up later and, at this examination, the blood type determinations possible at that time (in the AB0 and MN system) were also undertaken.

Following the rapid progress in serology which has occurred since *Essen-Möller*'s investigation was undertaken, the number of definite criteria of dizygosity has increased very considerably. In an extensive work, *Breitinger* (1952) outlined the status of the diagnosis of zygosity at that time. According to *Breitinger*, the diagnosis of zygosity consists of three methodologically different components: firstly, the demonstration of monozygosity by means of the examination of the afterbirth, if possible, which is the only way to obtain a *proof of monozygosity*. Secondly, a number of criteria permits a *diagnosis of genetic difference* ("Diskordanz-Diagnose"), which is directed towards the demonstration of dizygosity. For this purpose both exact and empirical aids are available. The *exact* diagnosis of genotypical dissimilarity is based upon genetically well-analyzed traits with a known mode of inheritance and a maximum degree of environmental stability. These traits possess the methodological advantage that even a monosymptomatic difference between two partners is proof of dizygosity. In addition to sex and blood groups, *Breitinger* includes in this category of criteria the PTC taste ability and the epidermis-factor established by *Bonnevie* which is reflected in the dermal ridge pattern of the finger tips. On a basis of *Mendel*'s Laws, the gene frequencies in the population and the ordinary calculations of probability *Breitinger* finds how frequently it should be possible to establish the diagnosis of dizygosity in a pair of twins taken from the population when the traits mentioned have been investigated

("Diskordanzerwartung"). A different group of criteria, e.g. hair colour, eye colour and a series of morphological traits may be employed in the diagnosis of difference with the same purpose, but the existence of geno-typical dissimilarity can only be inferred empirically, not directly. These empirical aids include traits with partially or completely unknown modes of inheritance and a slighter degree of environmental stability. In this respect, preliminary systematic investigations are required to elucidate the degree of variation between the partners of the two twin types. As emphasized by *Breitinger*, these investigations ought to be carried out in accordance with the principles adopted by *Essen-Möller*. Generally spoken, these empirically grounded criteria belong to another class than the aids for the exact diagnosis of difference, as they only occasionally permit a definite diagnosis of dizygosity. It is also more difficult to combine these criteria as correlation between two or more may exist.

The polysymptomatic *similarity test* is the third and last resort in the determination of zygosity. This test aims at demonstrating monozygosity; from an extensive phenotypical agreement the identity in the supposed corresponding genes is deduced and from this partial genotypical identity the probability of monozygosity (complete genotypical identity) may be estimated. As *Breitinger* also maintains, this test will become increasingly less necessary as attempts must primarily be made to develop the means of the diagnosis of genetic difference to such an extent that practically all dizygotic twins are classified in this manner and, therefore, independently of the similarity test. Prior to the development of serology only sex was available as proof of dizygosity, and among twins of the same sex the dizygotic twins appeared only in the mixed residue in which the similarity test did not demonstrate "adequate" similarity.

Breitinger did not carry out any more detailed analysis of the estimation of monozygosity; this aspect was, on the other hand, treated by *Smith* and *Penrose* (1954/55) in a very valuable work based partially upon the same principles as mentioned above which *Fisher* (1951) had already stated, and the analysis of the scope of the zygosity diagnosis was hereby extended and supplemented.

In the work by *Smith* and *Penrose* the estimation of the probability for monozygosity in a given pair of twins (with or without knowledge of the genotypes of the parents) is reviewed as this is required when the definite dizygotic pairs have been excluded by means of the diagnosis of genetic difference. The estimation, as in *Breitinger*'s empirical diagnosis of difference, is based upon knowledge obtained previously of the incidence of differences between the measurements of a given trait in the two types of

twins. While *Breitinger* was only concerned with the potential value of the traits for the demonstration of dizygosity, *Smith* and *Penrose* supply the complete calculations of the relative chances in favour of dizygosity in a given pair when the partners show identity in a given character. Concerning blood groups with their known mode of inheritance and marked environmental stability, the calculations are simplified by the presumption that monozygotic twins always show the difference 0; the problem then becomes only to find the frequency with which a dizygotic twin has a partner with similar phenotype, and this is equivalent to the probability that two siblings show identity. For each of the current blood group systems, *Smith* and *Penrose* present in tabular form the relative chances in favour of dizygosity when the two partners are identical in this respect. If the blood groups of the parents are unknown the calculations are based upon the gene frequencies in the ordinary population. In addition, the relative chances of dizygosity in a pair presenting a given difference in the dermal ridge pattern of the finger tips (expressed as the total ridge count), in the sums of the maximal palmar angles, in stature and in cephalic index are tabulated. It is emphasized that the figures, on which these calculations are based, are not very extensive and partly inadequate. By a combination of the relative chances in favour of dizygosity thus obtained, and the basic probability of occurrence of the two types of twins, the absolute probability of dizygosity (or monozygosity, respectively) may be found after the similarity test has been carried out concerning all the traits mentioned.

Similarly, *Sutton*, *Clark* and *Schull* (1955) have also dealt with the calculation of probability for monozygosity in a given pair who shows identity as regards a series of traits and they proceed according to the same principles as mentioned above. These authors are concerned both with the situation in which the genotypes of the parents are completely or partially known and also the situation which occurs most frequently, that information concerning the possible phenotypes of the parents can only be obtained from the phenotypes of the twins and the gene frequencies in the population. They supply simple formulae for the calculation of the total probability of identity in a series of independent loci. They only deal with traits concerning which the genetic mechanism is known.

Thus, the statistical principles to be adopted in the zygosity diagnosis are fully elucidated and instructions for the practical treatment of the information obtained by the serological investigations of a given twin pair have been presented. It seems, however, appropriate to consider a few of the statistical problems involved in the estimation of zygosity in more detail and, furthermore, to investigate the agreement between the cal-

Table 1

Composite distribution of the probability of identity of two sibs

Column   I: Probability of identity of two sibs   Column II: Frequency
Column III: Number of segregation groups

I	II	III	I	II	III	I	II	III
.50000	.000446	2	.01717	.000516	144	.00429	.000256	576
.31250	.000974	4	.01648	.000483	108	.00412	.000198	432
.25000	.004666	4	.01562	.049348	64	.00402	.000000	864
.19531	.000847	8	.01526	.007172	128	.00391	.008782	256
.18750	.001501	6	.01490	.000000	256	.00381	.001441	512
.15625	.009044	8	.01465	.044177	96	.00366	.008056	384
.12500	.019777	8	.01431	.000353	192	.00358	.000036	768
.12207	.000368	16	.01373	.003949	144	.00343	.000808	576
.11719	.002984	12	.01318	.000535	108	.00330	.000078	432
.09766	.006800	16	.01221	.029236	128	.00322	.000009	864
.09375	.010655	12	.01192	.000020	256	.00305	.004097	512
.07812	.033475	16	.01172	.029152	96	.00298	.000001	1024
.07629	.000080	32	.01144	.003971	192	.00293	.003323	384
.07324	.002301	24	.01118	.000000	384	.00286	.000431	768
.07031	.001452	18	.01099	.008674	144	.00275	.000904	576
.06250	.044554	16	.01073	.000058	288	.00268	.000001	1152
.06104	.002452	32	.01030	.000238	216	.00257	.000022	864
.05859	.018274	24	.00977	.047950	128	.00244	.004639	512
.04883	.021202	32	.00954	.000530	256	.00238	.000022	1024
.04768	.000007	64	.00916	.016395	192	.00229	.001222	768
.04688	.028602	24	.00894	.000004	384	.00220	.000331	576
.04578	.000853	48	.00879	.005391	144	.00215	.000029	1152
.04395	.002605	36	.00858	.000677	288	.00206	.000021	864
.03906	.064472	32	.00824	.000556	216	.00195	.001791	512
.03815	.000417	64	.00781	.026159	128	.00191	.000218	1024
.03662	.011637	48	.00763	.004455	256	.00183	.001289	768
.03516	.005736	36	.00745	.000000	512	.00179	.000002	1536
.03125	.059355	32	.00732	.025581	192	.00172	.000076	1152
.03052	.006050	64	.00715	.000216	384	.00165	.000006	864
.02980	.000000	128	.00687	.002845	288	.00153	.000579	1024
.02930	.040842	48	.00671	.000000	576	.00146	.000452	768
.02861	.000148	96	.00659	.000314	216	.00143	.000033	1536
.02747	.001742	72	.00644	.000040	432	.00137	.000073	1152
.02637	.000327	54	.00610	.014661	256	.00122	.000588	1024
.02441	.033372	64	.00596	.000005	512	.00119	.000001	2048
.02384	.000027	128	.00586	.012942	192	.00114	.000086	1536
.02341	.038199	48	.00572	.002025	384	.00110	.000022	1152
.02289	.063274	96	.00549	.004432	288	.00098	.000200	1024
.02197	.008180	72	.00536	.000016	576	.00095	.000012	2048
.01953	.071600	64	.00515	.000161	432	.00092	.000081	1536
.01907	.000712	128	.00488	.019478	256	.00076	.000032	2048
.01863	.000000	256	.00477	.000175	512	.00073	.000025	1536
.01831	.020363	96	.00458	.000517	384	.00061	.000030	2048
.01788	.000009	192	.00447	.000001	768	.00049	.000009	2048
.01758	.008005	72	.00439	.001894	288	Total	1.000000	

culated probabilities of identity between two sibs and the actual incidence of identical sib pairs in a collection of sibships. These two points will be treated below and it will be shown that it appears justifiable to presume that the observed number of sib pairs showing identity with regard to a given series of characters is in agreement with expectation, calculated according to the principles outlined here.

Calculating the chance of monozygosity in a given pair of twins, the fact that the individual probabilities involved in the final product may vary greatly should be taken into consideration. The distribution of the individual probabilities may, however, be deduced.

The combined probability of identity between two siblings in all the blood group systems employed and sex is found as the product of the probability of identity within each of these traits and this also holds true as regards the frequency of the segregation types. This is only the case when the corresponding genes are independent of each other, a presumption which seems to be justified concerning the traits mentioned here with the exception of the Lutheran and Lewis systems. The effect of the probable linkage between these two loci in calculating the combined probability when both of these systems are included will be discussed in more detail in a subsequent paper.

Employing these principles, the complete distribution of the probability of identity between two siblings may be reviewed. In tabular form (Table 1) this distribution is not particularly employable in practice as a new genetic system cannot simply be inserted nor can it be adjusted to other gene frequencies than those employed here.*)

An attempt has therefore been made to find a simplified approximate calculation. On account of the extent of the serological investigations of the material mentioned below only seven blood group systems and sex have been included in the numerical calculations.

As the point of commencement for the approximation it is presumed that the probability P that two siblings are identical in respect of all systems, is found by multiplying the probabilities P_i that the siblings are identical in respect of the individual system, i. Thus, the following equation is obtained

$$P = \prod_{i=1}^{n} P_i$$

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*) In the numerical computations the following gene frequencies have been used: O: 0.6508, A_1: 0.2030, A_2: 0.0718, B: 0.0744. MS: 0.2007, Ms: 0.3305, NS: 0.0681, Ns: 0.4007. P: 0.533, p: 0.467. r: 0.3891, R_1: 0.4215, R_2: 0.1505, R_0: 0.0181, R': 0.0125, R": 0.0074, R_z: 0.0009, R_y: 0.0000. The frequencies given here are those which have been used by the University Institute of Forensic Medicine, Copenhagen, based on their material of Danish individuals (*Gürtler*, personal communication). – Fy^a: 0.4630, Fy^b: 0.5370 (*Mohr*, Denmark, 1953–54). Le^a: 0.4731, Le: 0.5269. Jk^a: 0.4982, Jk^b: 0.5018 (*Race* and *Sanger*, England, 1954). K: 0.0461, k: 0.9539 (*Heistö*, Norway, 1955). Lu^a: 0.0428, Lu^b: 0.9572 (*Mohr*, Denmark, 1954). – Hp^1: 0.403, Hp^2: 0.597 (*Galatius-Jensen*, Denmark, 1957). Gm^a: 0.334, Gm: 0.666 (*Linnet-Jepsen*, *Galatius-Jensen* and *Hauge*, Denmark, 1958).

If the logarithm of each side of the equation is taken, then:

$$\log P = \sum_{i=1}^{n} \log P_i .$$

According to the central limit theorem it will be found that a sum of stochastic variables with approximation will be normally distributed with a mean equal to the sum of the means of the individual stochastic variables and a variance which is equal to the sum of the variances of the individual stochastic variables. In order to obtain good approximation the number of variables must be relatively large.

In order to investigate how the approximation becomes with the eight factors involved here, the mean and the variance of the logarithm of the probability that two siblings are identical are calculated for each individual system per se and for all systems together commencing from the values recorded in Table 1. The results are recorded in Table 2.

Table 2

Mean and variance of the logarithm of the probability of identity of two sibs
given for seven blood group systems and sex

		Mean	Variance
Sex		— 0.3010	0.00000
Rhesus		— 0.3529	0.03353
A_1A_2B0		— 0.2479	0.03045
MNS		— 0.3550	0.03128
P		— 0.1159	0.01655
Lewis		— 0.1179	0.01667
Duffy		— 0.1368	0.01758
Kell		— 0.0498	0.01235
	Sum	— 1.6772	0.15841
Computed from the composite distribution:			
		— 1.6771	0.15849

It will be observed that the sum of the means for the individual system is — 1.6772 and that the mean for all of the systems together is — 1.6771. Correspondingly, the variances are 0.1584 and 0.1585, respectively. In Figure 1 the distribution recorded in Table 1 is plotted in a probit diagram, the logarithm of a probability for identity being represented along the horizontal axis and the distribution appearing as a stepped curve. The straight line represents the normal distribution, the mean and variance of which has just been recorded. It will be observed that the approximation must be regarded as satisfactory for the present object but it should, however, be borne in mind that in this case a discontinuous distribution is approximated to the continuous normal distribution.
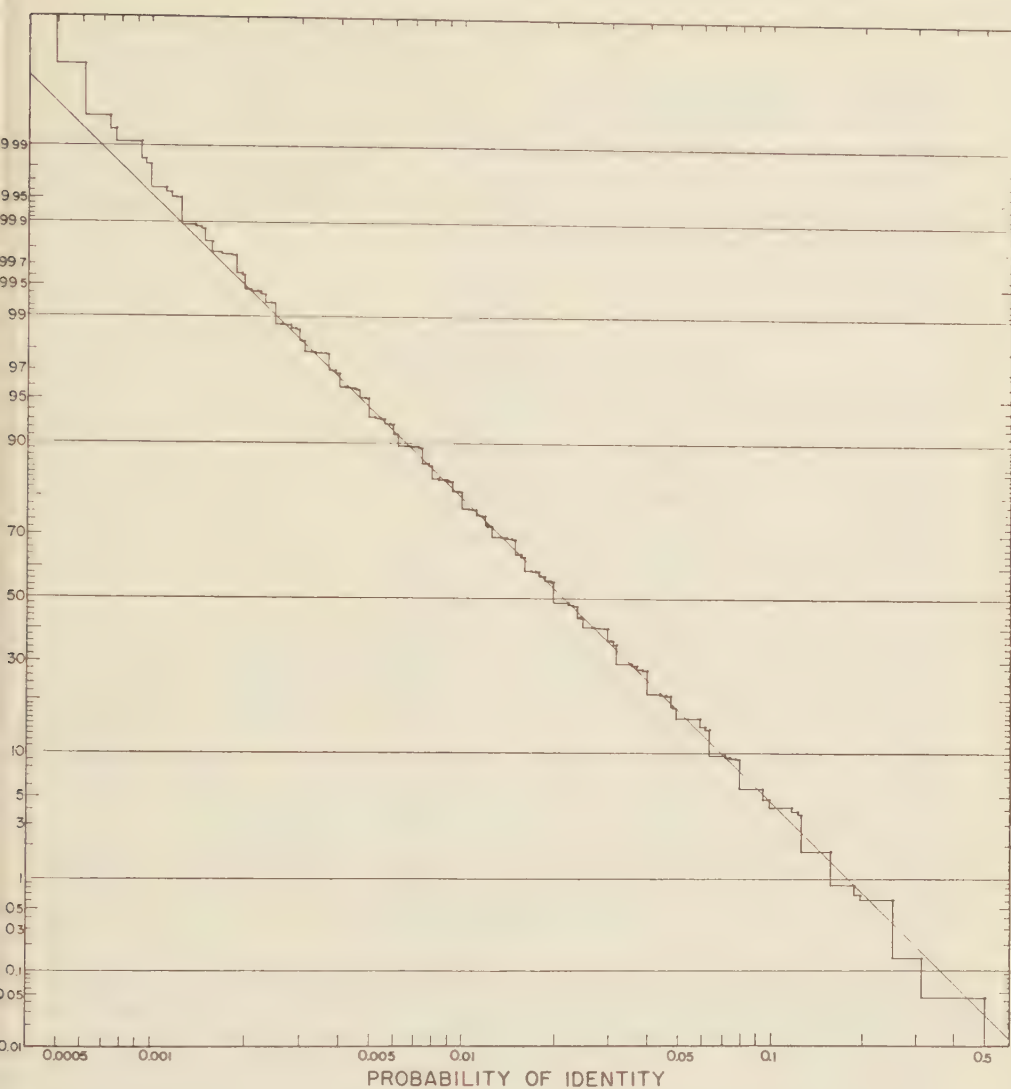
Figure 1

Composite distribution of the probability of identity of two sibs
compared with the corresponding normal distribution

Starting from the mean and the variance of the logarithmic values for the probability
of identity between two siblings, the arithmetic mean of the probabilities may be cal-
culated with the help of the formula:

$$\log M \left\{ P \right\} = M \left\{ \log P \right\} + 1.1513 \, V \left\{ \log P \right\},$$

in which M and V indicate the mean and the variance, respectively. If the formula is employed in this case, then $M \left\{ P \right\} = 0.0320$ is obtained while direct calculation from Table 1 gives a value of 0.0319.

In order to investigate whether the average probability of the identity between two siblings, calculated to 0.0319 from the gene frequencies recorded earlier, corresponds also to that observed in the population, a material of sibships has been analyzed all of whom had been examined on account of some hereditary disease in the family. In the material, all parts of Denmark are represented.

Table 3

Comparison between observed and expected number of identical sibs
in a material of 263 sibships

Number of sibs in sibship	Number of sibships	Number of paired sibs	Number of identical pairs			obs—exp. stand. dev.
			observed	expected	Standard dev.	
2	73	73	2	2.33	1.50	— 0.22
3	65	195	1	6.22	2.57	— 2.03
4	45	270	13	8.61	3.21	1.37
5	34	340	10	10.85	3.86	— 0.22
6	24	360	10	11.48	4.25	— 0.35
7	7	147	2	4.69	2.93	— 0.92
8	6	168	2	5.36	3.37	— 1.00
9	5	180	4	5.74	3.75	— 0.46
10	1	45	2	1.44	2.01	0.28
11	2	110	4	3.51	3.36	0.15
12	1	66	2	2.11	2.78	— 0.04
Total	263	1954	52	62.34	$\dfrac{52 - 62.34}{10.49} =$	— 0.99

Table 3 indicates the composition of the material collected. In the first column the size of the sibship is given. In the second column the corresponding number of sibships observed is recorded. From these columns, the third column is calculated as in a sibship of k siblings there are $\frac{1}{2}$ k (k—1) pairs of siblings. The material comprizes a total of 1,954 pairs of siblings. In the fourth column is recorded how many of the pairs of siblings were identical, a total of 52 being found, and the fifth column shows how many are expected when the mean probability is 0.0319, viz, a total of 62.34. In the sixth column the standard deviation of the values observed is recorded. In the Appendix the variance of the observed identical pairs in a family consisting of k individuals is deduced (Formula (4)) and by employment of the values calculated from Table 1 the formula becomes:

$$V \left\{ x \right\} = \tfrac{1}{2} k (k-1) \left[0.02965 + (2k-4) 0.00026 + \tfrac{1}{2} k (k-1) 0.00124 \right] .$$

Table 4 records how this variance and standard deviation of the individual pairs depends upon the size of the sibship.

Table 4

Variance and standard deviation for a single pair of sibs
according to the number of individuals in the sibship

Number of individuals in sibship	Variance	Standard deviation
2	0.03089	0.176
3	0.03389	0.184
4	0.03813	0.195
5	0.04381	0.209
6	0.05033	0.224
7	0.05829	0.241
8	0.06749	0.260
9	0.07793	0.279
10	0.08961	0.299
11	0.10253	0.320
12	0.11669	0.342

Finally, in the seventh column of Table 3 the difference between the observed and expected number of identical pairs divided by the standard deviation is recorded. It appears that none of the values is numerically greater than 2.03, viz, in no case is there a significant difference between the observed and the expected numbers. This holds also true concerning the comparison between the total number of observed and expected pairs where the value is — 0.99.

The combined probability, P, of identity of two sibs as regards the seven blood groups mentioned above and sex, which is found to be 0.032, opens a possibility of estimating the total number of dizygotic twins in a representative collection of twins.

If the sampling of twins is random as far as sex and blood groups are concerned and assuming that the distribution of dizygotic twins in these respects do not differ from the general population one finds that the number of dizygotic twins observed in the sample, d say, presenting non-identity of the traits mentioned, is a fraction, $1 - P$, of the total number of dizygotic twins in the material, m. An estimate of m is obtained by the formula:

$$m = d \,/\, 1 - P.$$

This is an extension of the formula used by *Weinberg* (1901) for the estimation of the number of dizygotic twins in an unselected sample of twins, based upon the criterion of sex alone.

The standard deviation of d is in this case (cf. Table 4) $\sqrt{0.03079\ m}$, and the confidence limit m_t of m is found from the identity:

$$m_t = d + t \sqrt{0.03079\ m_t} \,/\, 0.968$$

t being the fractile in the normal distribution with mean 0 and variance 1 which corresponds to the confidence wanted. Generally, with reasonably large values of d and of $m - d$ it is possible to use m instead of m_t on the right side of the equation.

Comment

Considering the scientific value and importance of twin investigations it is obvious that as far as possible all the available criteria which permit exact diagnosis of dizygosity should be employed.

If the present possibilities for twin diagnosis be summarized it will be found, first and foremost, by calculations according to the principles mentioned that by use of sex, eight blood group systems (A_1A_2B0, MNS, Rhesus [with five sera], P, Lewis, Kell, Lutheran and Duffy) and two serum group systems (Haptoglobin and Gamma) the probability of establishing the diagnosis of dizygosity is **98.01** per cent., i.e. that of all pairs of dizygotic twins from the ordinary (Danish) population, 98.01 per cent. may be placed in the correct group by means of the diagnosis of genetic difference when this is completely utilized. If the Kidd system also is included, the percentage increases to 98.45. The percentages hold true provided that no linkage between the systems exist.

By utilizing all the serological possibilities, a large group of definite dizygotic twins is obtained, comprizing practically all, and, thus, better representation of the extent of variation between dizygotic twin partners. Simultaneously, an improved basis is built up for the estimation of the absolute probability of monozygosity in the pairs which are similar as regards the traits concerned. At this point the empirically based criteria of the similarity test may be invoked to obtain a further increase of the accuracy. By omitting the serological factors, it must be borne in mind that the position is much weaker in respect of the criticism frequently levelled at the solution of the zygosity problems. The twin method involves, in advance, so many problems and sources of error that the existing possibilities should be utilized in order to reduce *one* of the important sources of error. The calculations recorded above clearly demonstrates the actual possibilities.

As regards the future development of twin diagnosis it appears obvious that it will be of the greatest significance to extend the diagnosis of genetic difference by attempting to elucidate the genetics of more of the normal traits.

It seems appropriate already now to revise the analysis particularly of the scope of the morphological traits considering the improvement in the subdivision of a representative twin material which the most recent serological findings offer. This will also occur concerning the material previously mentioned, collected and analyzed by *Essen-Möller*. *Essen-Möller*'s coworkers have undertaken a renewed investigation of the surviving twin

pairs, who were found to be similar as regards sex and the AB0 and MN systems at the first examination. It has proved possible to renew contact with all of them as the result of the excellent system of registration in Sweden. After complete employment of the existing possibilities of the diagnosis of genetic difference the value of the other criteria can be subjected to revision. In this connection, investigation of the PTC taste ability will also be of interest as various observations in recent years suggest that absolute proof value possibly cannot be assigned to this ability as with blood groups. It appears that not all of the phenotypic variability in taste sensitivity is genetically determined (cf. e.g. *Merton*, 1958).

When the results of the revision mentioned are presented, the twin diagnosis may be considered to have been brought on a level with the current development of that section of human genetics which is of direct practical value for the problems of zygosity.

Summary

In a survey of the basic methodological problems concerning zygosity diagnosis in twins the value of employing extensive serological investigations is emphasized. It is calculated that the use of the blood and serum groups now available permits an exact diagnosis of dizygosity in about 98 per cent. of all dizygotic twin pairs.

Zusammenfassung

Es wird ein Überblick über die grundlegenden methodologischen Probleme der Eiigkeitsdiagnose bei Zwillingen gegeben. Dabei wird der Wert ausgiebiger serologischer Untersuchungen betont. Berechnungen ergeben, dass der Gebrauch der Blutfaktoren und Serum-Proteingruppen, die jetzt zur Verfügung stehen, eine exakte Diagnose der Zweieiigkeit in ca. 98% aller zweieiigen Zwillingspaare gestattet.

Résumé

Les auteurs soulignent l'importance des examens sérologiques étendus pour le diagnostic des jumeaux univitellins et bivitellins. En tenant compte

des différents groupes dans le sang et le sérum, les calculs ont démontré qu'on peut obtenir aujourd'hui un diagnostic exact des jumeaux bivitellins dans 98% de tous les jumeaux dizygotiques.

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Appendix

Mean and variance of the number of identical pairs in a sibship comprising k individuals

In a sibship comprising k individuals we can pair the sibs in $\frac{1}{2}$ k (k—1) ways.

In the following a given combination of segregation rates is assumed. The number of possible phenotypes of the children is called n, the probability (the segregation rate) that a child will be of phenotype μ is called p_μ. μ can be one of the numbers from 1 to n.

We can find the probability that

a_1 of the children are of phenotype 1

a_2 of the children are of phenotype 2

. . . . .

a_n of the children are of phenotype n, where $\sum\limits_{\mu=1}^{n} a_\mu = k$.

This probability is

$$\frac{k!}{a_1! \, a_2! \ldots \ldots a_n!} \, p_1{}^{a_1} p_2{}^{a_2} \ldots \ldots p_n{}^{a_n}$$

The number of identical pairs is called x and for the sibship in question this number is

$$x = \sum_{\mu=1}^{n} \tfrac{1}{2} a_\mu (a_\mu - 1).$$

The mean of x will then be

$$M\left\{x\right\} = \sum_{\substack{\sum\limits_{\mu=1}^{n} a_\mu = k}} \frac{k!}{a_1! a_2! \ldots \ldots a_n!} p_1{}^{a_1} p_2{}^{a_2} \ldots p_n{}^{a_n} \sum_{\mu=1}^{n} \tfrac{1}{2} a_\mu (a_\mu - 1),$$

where the first summation is extended to all combinations of a_μ's with the sum k. The order of summations can be changed and we find

$$M\left\{x\right\} = \frac{1}{2} \sum_{\mu=1}^{n} \sum_{a_\mu=0}^{k} \binom{k}{a_\mu} p_\mu^{a_\mu} (1-p_\mu)^{k-a_\mu} a_\mu (a_\mu-1)$$

$$= \frac{1}{2} k (k-1) \sum_{\mu=1}^{n} p^2_\mu \sum_{a_\mu=2}^{k} \binom{k-2}{a_\mu-2} p_\mu^{a_\mu-2} (1-p_\mu)^{k-a_\mu}$$

$$(1) \qquad = \frac{1}{2} k (k-1) \sum_{\mu=1}^{n} p^2_\mu$$

This is the expected number of identical pairs in a sibship comprising k individuals. It is seen that the formula is as usual: the expected number of pairs of sibs is equal to the probability $\sum_{\mu=1}^{n} p^2_\mu$ that two sibs are identical multiplied with the number of pairs of sibs $\frac{1}{2}$ k (k—1) in the sibship.

The variance of x can be found by the formula

$$V\left\{x\right\} = \sum_{\substack{\sum_{\mu=1}^{n} a_\mu = k}} \frac{k!}{a_1! a_2! \ldots a_n!} p_1^{a_1} p_2^{a_2} \ldots p_n^{a_n} \left[\sum_{\mu=1}^{n} \frac{1}{2} a_\mu (a_\mu-1)\right]^2 -$$

$$- \left[M\left\{x\right\}\right]^2$$

By computations similar to those by which the mean was found we see that

$$(2) \qquad V\left\{x\right\} = \frac{1}{2} k (k-1) \left[\sum_{\mu=1}^{n} p^2_\mu (1 - \sum_{\mu=1}^{n} p_\mu^2) + (2 k-4) \sum_{\mu=1}^{n} p^2_\mu \right.$$

$$\left. (p_\mu - \sum_{\nu=1}^{n} p_\nu^2)\right].$$

If the pairs of sibs in the sibship had been stochastically independent we would have the variance

$$V\left\{x\right\} = \tfrac{1}{2}k\,(k-1)\sum_{\mu=1}^{n}p^2{}_{\mu}\,(1-\sum_{\mu=1}^{n}p^2{}_{\mu}).$$

This is the first term in the formula. To this we must add a correction which is zero when $k = 2$. It can be shown that if $k \geq 3$ the correction is greater than zero except in the case where the probabilities p_μ (the segregation rates) for the n phenotypes are equal.

In the preceding it was presumed that the combination of segregation rates was known. The problem is now to find the variance for a sibship comprising k individuals but where the only information available concerning the combination of segregation rates is that they are distributed as in the general population.

With the notation γ for a given combination of segregation rates which in the general population has the frequency h_γ we can find the variance of the observed number of identical pairs x_ν from the formula

(3)
$$V\left\{x\right\} = \sum_{\nu=1}^{\tfrac{1}{2}k\,(k-1)}\sum_{\gamma}(x_\nu-\overline{x})^2\,h_\gamma\,P\left\{x_\nu\,\middle|\,\gamma\right\},$$

where we have to sum γ over all possible combinations of segregation rates in the general population. We then have that $\Sigma h_\gamma = 1$, and (3) will give us

(4)
$$V\left\{x\right\} = \sum_{\gamma}h_\gamma\,V\left\{x\,\middle|\,\gamma\right\} + \sum_{\gamma}h_\gamma\,(\overline{x}_\gamma-\overline{x})^2,$$

where $V\{x\,\gamma\}$ is the variance for a given combination of segregation rates as shown in (2) and $\overline{x}_\gamma$ is the expected number of identical pairs for a given combination of segregation rates. The last term is the variance of the expected number of identical pairs in the general population equal to $[\tfrac{1}{2}k\,(k-1)]^2$ times the variance in the general population of the probability that a pair of sibs is identical.

Aus dem Max Planck-Institut für vergleichende Erbbiologie und Erbpathologie
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EIN STATISTISCHER GESICHTSPUNKT FÜR DAS PLANEN VON UNTERSUCHUNGEN ÜBER ÄNDERUNGEN DER MUTATIONSRATE BEIM MENSCHEN

Von DIETRICH STROBEL und FRIEDRICH VOGEL

1. Das Problem

Eine der brennendsten Fragen, vor die sich die Humangenetik heute gestellt sieht, lautet: In welchem Maße nimmt die Mutationsrate menschlicher Gene infolge der verschiedenen zivilisatorischen Einflüsse, also insbesondere mit der vermehrten Exposition gegenüber ionisierenden Strahlen zu? Aus verschiedenen Gründen (vgl. *Nachtsheim* 1957; *Vogel* 1958) ist es kaum möglich, aus den bisherigen experimentellen Erfahrungen bei Tieren, Pflanzen und Mikroorganismen quantitative Rückschlüsse auf den Menschen zu ziehen. Wir müssen deshalb das Problem beim Menschen selbst zu untersuchen anstreben. Unter den verschiedenen hier möglichen Ansatzpunkten (vgl. *Neel* u. Mitarb. 1956) heben sich zwei heraus, von denen ausgehend man mit einiger Sicherheit genetische Effekte zu erfassen hoffen darf: Die Untersuchung des Geschlechtsverhältnisses bei der Geburt (vgl. *Neel* u. Mitarb. 1956; *Lejeune* u. *Turpin* 1957 u. a.) und die Bestimmung von Mutationsraten einzelner wohldefinierter dominanter und geschlechtsgebunden-rezessiver Gene (*Haldane* 1935; *Gunther* u. *Penrose* 1935; Lit. bei *Neel* 1952, *Nachtsheim* 1954; *Vogel* 1954; *Neel* u. Mitarb. 1956; *Penrose* 1957; *Becker* 1958 u. v. a.). Dieses letzte Verfahren übertrifft vom theoretischen Ansatz her an Zuverlässigkeit alle anderen; es soll daher hier allein abgehandelt werden. Wir möchten aber ausdrücklich betonen, daß wir als ergänzende Methode – trotz der Schwierigkeiten beim Deuten der Be-

funde – auch die Prüfung des Geschlechtsverhältnisses als sehr wertvoll ansehen. Nur bedarf es hier, wenn man untersuchen will, ob die Mutationsrate in der allgemeinen Bevölkerung zunimmt, keiner besonderen Planung; die allgemeine Bevölkerungsstatistik ist in der Lage, die notwendigen Daten bereitzustellen.

Dagegen müssen Untersuchungen über Veränderungen in der Mutationsrate einzelner, gut definierter dominanter und x-chromosomal rezessiver Gene sorgfältig geplant werden, damit sie überhaupt sinnvolle Resultate ergeben. Für diese Planung können die bisherigen Arbeiten über Mutationsraten einzelner Gene vor allem in zwei Richtungen als «pilot investigations» dienen: Einmal wurde man sich mit ihrer Hilfe über die Fehlerquellen der vorliegenden Methoden klar und lernte die Voraussetzungen kennen, die Mutationen mitbringen müssen, damit man ihre Mutationsraten mit einiger Genauigkeit berechnen kann. (U.a. *Haldane* 1949; *Nachtsheim* 1954; *Vogel* 1954; *Stevenson* 1957.) Dieser Gesichtspunkt wird in dieser Arbeit nur kurz erwähnt werden.

Zweitens geben die bisherigen Arbeiten uns einen ungefähren Anhaltspunkt über die Anzahl von Neumutanten geeigneter Gene, die man in menschlichen Bevölkerungen zu erwarten hat. Dadurch helfen sie mit, eine statistische Voraussetzung für das Planen derartiger Untersuchungen zu schaffen. Sie erlauben es, wenigstens größenordnungsmäßig die Frage zu behandeln: Auf eine wie große Bevölkerung muß sich eine solche Untersuchung erstrecken, wenn ich einen Trend der Mutationsrate in der Zeit mit einer bestimmten Genauigkeit erfassen will? Es ist überaus wichtig, daß man sich diese Frage beantwortet, bevor man größere, arbeitsreiche und kostspielige Untersuchungen plant. Allzu leicht kann es sonst geschehen, daß große Mittel und viel Arbeit umsonst vertan werden, weil man nachträglich feststellt, daß etwa die Bevölkerung, von der man ausging, viel zu klein war.

Dieses Problem soll hier vor allem abgehandelt werden.

2. Das mathematische Modell

Der eine von uns (D.S.) entwickelte kürzlich in ganz anderem Zusammenhang ein mathematisches Modell, das er verwendet, wenn er einen Trend im Verkauf bestimmter Konsumgüter (z.B. Zahnpastatuben) beurteilen will. Dieses Modell läßt sich auch auf das hier vorliegende Problem anwenden. Wir machen dabei zwei vereinfachende Annahmen:

a) Die Bevölkerungsgröße und vor allem die Geburtenziffer bleibe im Untersuchungszeitraum gleich. – Diese Annahme trifft in westeuropäischen

Bevölkerungen größenordnungsmäßig zu; eine Abweichung läßt sich sehr leicht rechnerisch berücksichtigen.

b) Wir legen der Beurteilung des Trends in der Mutationsrate zwei Stichproben zugrunde, die zu verschiedenen Zeiten bei der gleichen Bevölkerung erhoben wurden. – In Wirklichkeit wird man eine kontinuierliche Erfassung der in Frage stehenden Merkmale für mehrere Jahrzehnte anstreben und dementsprechend auch die Endauswertung einrichten. Das berührt aber das Ergebnis der hier angestellten Betrachtungen praktisch nicht.

Wir führen folgende Bezeichnungen ein:

μ_1 = Mutationsrate zur Zeit der ersten Beobachtung.

μ_2 = Mutationsrate zur Zeit der zweiten Beobachtung.

t = $\dfrac{\mu_2}{\mu_1}$ — Der Trend in der Mutationsrate, z. B. Erhöhung oder Erniedrigung.

x_1 = Zahl der Neumutanten in der ersten Bevölkerungs-Stichprobe.

x_2 = Zahl der Neumutanten in der zweiten Bevölkerungs-Stichprobe.

$x_{1,2}$ = $x_1 + x_2$ = Summe aller Neumutanten beider Stichproben.

t' = $\dfrac{x_2}{x_1}$ = Der in der Stichprobe beobachtete Trend.

Ist $x_{1,2}$ gegeben, so sind die Erwartungswerte von x_1 und x_2:

$$(1) \qquad E(x_1) = \frac{x_{1,2}}{1 + t} \; ; \qquad\qquad E(x_2) = \frac{t x_{1,2}}{1 + t} .$$

Die gefundenen Werte x_1 und x_2 lassen sich nun mit diesen Erwartungswerten vergleichen:

$$(2) \qquad \chi^2 = \frac{\left(x_1 - \dfrac{x_{1,2}}{1+t} \right)^2}{\dfrac{x_{1,2}}{1+t}} + \frac{\left(x_2 - \dfrac{t x_{1,2}}{1+t} \right)^2}{\dfrac{t x_{1,2}}{1+t}} .$$

Aus der Gleichung

$$(3) \qquad\qquad P(\chi^2 < \chi_0^2) = \alpha$$

mit einem vorgegebenen Vertrauensbereich α läßt sich χ_0^2 für einen Freiheitsgrad aus einer χ^2-Tafel entnehmen. Entsprechend der Beziehung $t' = \dfrac{x_2}{x_1}$ setzen wir jetzt ein:

$$x_1 = \frac{x_{1,2}}{1 + t'} \; ; \qquad\qquad x_2 = \frac{t' x_{1,2}}{1 + t'} .$$

Wir erhalten die Ungleichung:

$$(4) \qquad \frac{\left(\dfrac{1}{1+t'} - \dfrac{1}{1+t} \right)^2}{\dfrac{1}{1+t}} + \frac{\left(\dfrac{t'}{1+t'} - \dfrac{t}{1+t} \right)^2}{\dfrac{t}{1+t}} < \frac{\chi_0^2}{x_{1,2}}$$

Damit haben wir einen Ausdruck für die Beziehung zwischen dem wahren Wert t des Mutationsraten-Trends und dem beobachteten Wert t' gewonnen. Diese Beziehung kann auf die Form reduziert werden:

$$(5) \qquad \frac{(t + t'^2)\,(1 + t)}{(1 + t')^2\, t} = \frac{1 + \chi_0^2}{x_{1,2}}\;.$$

Für ein bestimmtes $x_{1,2}$ und ein vorgegebenes χ_0^2 bestimmt diese Ungleichung einen Bereich in der t,t'-Fläche, dessen Rand die Vertrauensgrenzen für das unbekannte t festlegt.

Löst man nach t' auf, so erhält man:

$$(6) \qquad t' = \frac{t\left(1 + \dfrac{\chi_0^2}{x_{1,2}}\right) \pm t\left(\sqrt{t} + \dfrac{1}{\sqrt{t}}\right)\sqrt{\dfrac{\chi_0^2}{x_{1,2}}}}{1 - t\,\dfrac{\chi_0^2}{x_{1,2}}}\;.$$

Der Term $\sqrt{t} + \dfrac{1}{\sqrt{t}}$ liegt sehr nahe bei 2, wenn t nicht allzu stark von 1 abweicht. Damit braucht man aber wie in den meisten Fällen, so auch beim Anstieg der Mutationsrate nicht zu rechnen. Auch $\dfrac{\chi_0^2}{x_{1,2}}$ ist sehr klein, wenn die Stichprobengröße nicht allzu gering ist. So ergibt sich näherungsweise:

$$(7) \qquad t'_{1,2} = t \pm 2\,t\,\sqrt{\frac{\chi_0^2}{x_{1,2}}}\;; \qquad \frac{|t'-t|}{t} = 2\,\sqrt{\frac{\chi_0^2}{x_{1,2}}}\;.$$

Aus dieser Gleichung lassen sich die Fehlergrenzen für t' leicht ermitteln. Vor allem aber ist es auch möglich, die Stichprobengröße zu errechnen, die notwendig ist, damit man einen Trend t mit einer bestimmten Genauigkeit erfassen kann. Gerade diese letzte Frage aber ist für unser Problem, die Planung von Mutationsraten-Untersuchungen, entscheidend wichtig. Deshalb stellten wir in Tab. 1 für eine Reihe von Werten für t und $x_{1,2}$ die sich ergebenden Fehlerbereiche für t'—t für ein vorgegebenes P = 0,95, $\chi^2(m=1) = 3,8$, zusammen. Die Werte wurden nach der Näherungsformel (7) errechnet. Will man sich einen Überblick über die Verhältnisse bei wesentlich geringerer Stichprobengröße verschaffen, so empfiehlt es sich, auf die Formel (6) zurückzugreifen.

Wollte man diese Formel (6) tabellieren, so müßte man je eine Tabelle für die obere und untere Grenze anlegen, da diese Formel eine Asymmetrie enthält. Man kann das umgehen, indem man den gesamten Bereich t'$_{max}$ — t'$_{min}$ angibt. Man erhält dafür aus Formel (6):

$$(6a) \qquad t'_{max} - t'_{min} - \frac{t\left(\sqrt{t} + \dfrac{1}{\sqrt{t}}\right)\sqrt{\dfrac{\chi_0^2}{x_{1,2}}}}{1 - t\,\dfrac{\chi_0^2}{x_{1,2}}}\;.$$

Tabelle 1

Werte für $|t' - t|$ in Abhängigkeit von t und von der gemeinsamen Größe der Stichproben $x_{1,2}$

t ↓	$x_{1,2}$ →									
	500	750	1000	1250	1500	1750	2000	2250	2500	2750
1,0	0,174	0,163	1,123	1,110	1,101	0,093	0,087	0,082	0,078	0,074
1,1	0,191	0,179	0,136	0,121	0,111	0,103	0,096	0,090	0,086	0,082
1,2	0,209	0,195	0,148	0,132	0,121	0,112	0,105	0,099	0,094	0,089
1,3	0,227	0,211	0,160	0,143	0,131	0,121	0,114	0,107	0,101	0,097
1,4	0,244	0,228	0,173	0,154	0,141	0,131	0,122	0,115	0,109	0,104
1,5	0,262	0,244	0,185	0,165	0,151	0,140	0,131	0,123	0,117	0,112

t ↓	$x_{1,2}$ →								
	3000	3500	4000	5000	6000	7000	8000	9000	10 000
1,0	0,071	0,066	0,062	0,055	0,050	0,047	0,043	0,041	0,039
1,1	0,078	0,073	0,068	0,061	0,055	0,051	0,048	0,045	0,043
1,2	0,085	0,079	0,074	0,066	0,060	0,056	0,052	0,049	0,047
1,3	0,093	0,086	0,080	0,072	0,065	0,061	0,056	0,053	0,051
1,4	0,100	0,092	0,087	0,077	0,070	0,065	0,061	0,057	0,055
1,5	0,107	0,100	0,093	0,083	0,075	0,070	0,065	0,062	0,059

Die größte Abweichung einer daraus errechneten halben Schwankungsbreite in dem in unserer Tab. 1 behandelten Bereich gegenüber den in dieser Tabelle berechneten Werten ergibt sich für $t = 1.5$, $x_{1,2} = 500$, nämlich 0.270 gegenüber 0.262 der Tabelle. Sie ist also für das vorliegende Problem unerheblich.

Obwohl es nicht unmittelbar zum Thema gehört, sei auch noch das Problem behandelt, wie umgekehrt für ein gefundenes t' die Vertrauensgrenzen berechnet werden. Zu diesem Zweck muß die Gleichung (5) nach t aufgelöst werden. Es ergibt sich:

$$(8) \qquad t_{\substack{max \\ min}} = t' + \frac{(1 + t')^2}{2} \frac{\chi_0^2}{x_{1,2}} \pm \sqrt{t'(1 + t')^2 \frac{\chi_0^2}{x_{1,2}} + \frac{(1 + t')^4}{4} \frac{\chi_0^4}{x^2_{1,2}}}.$$

Dabei wäre das 2. Glied unter der Wurzel ohne weiteres zu vernachlässigen.

Eine durchaus brauchbare Näherung erhält man, wenn man die Gleichung (7) nach t auflöst. Es ergibt sich:

$$(7a) \qquad \overline{t} = \frac{t'}{1 - 2\sqrt{\dfrac{\chi_0^2}{x_{1,2}}}} \quad ; \quad \underline{t} = \frac{t'}{1 \cdot 2\sqrt{\dfrac{\chi_0^2}{x_{1,2}}}}.$$

3. Die praktische Anwendung dieses Modells auf das Problem des
Mutationsraten-Trends

Damit wir aus diesem Modell die Konsequenzen für die praktische Planung ziehen können, müssen wir uns zunächst zwei Fragen vorlegen. Zunächst: Welche Merkmale eignen sich für die Bestimmung der Mutationsrate? Danach: Wie häufig kommen diese Merkmale ungefähr als Neumutanten vor?

Zur ersten Frage: Voraussetzung für einen Vergleich ist, daß praktisch jede Neumutante als solche erkennbar sein muß. Es kommen also nur solche Merkmale in Frage, die dominant vererbt werden. (Ein Merkmal, das hier wegen besonders günstiger Nebenumstände eine Ausnahme macht, vgl. unten.)

Weitere Voraussetzungen sind:

1. Die Penetranz muß vollständig oder doch praktisch vollständig sein.

2. Das Merkmal muß eindeutig diagnostizierbar und von verwandten Formen gut abzugrenzen sein. Die Abgrenzbarkeit von genetisch anderen Formen ist nicht so vordringlich, wenn diese Formen ebenfalls dominanten Erbgang haben (Beispiel: Die beiden Formen der Chondrodysplasie mit und ohne Beteiligung des Gesichtsschädels). Die Frage wird aber brennend, wenn es neben der dominanten etwa eine phänotypisch gleiche rezessive Form gibt.

3. Das Merkmal muß einen deutlichen Selektionsnachteil gegenüber dem Bevölkerungsdurchschnitt mit sich bringen. Sonst hat man nicht mit einer im Verhältnis zur Gesamtzahl der Patienten wesentlichen Anzahl von Neumutanten zu rechnen. Außerdem wächst die Bedeutung der Illegitimität als Fehlerquelle, wenn dieses Verhältnis der Neumutanten zur Gesamtzahl der Merkmalsträger abnimmt.

4. Man muß sicher sein, daß nach menschlichem Ermessen keine phänotypisch unabgrenzbaren Phänokopien vorkommen.

5. Es ist sehr günstig, wenn das Merkmal in jedem Falle zu ärztlicher Behandlung führt, da man über Ärzte, Krankenhäuser usw. am ehesten an die Fälle herankommt.

6. Das Merkmal darf nicht extrem selten sein.

Diese Voraussetzungen erscheinen relativ einfach. Prüft man aber die bekannten dominant erblichen Merkmale des Menschen daraufhin durch, welche von ihnen diese Voraussetzungen erfüllen, so findet man, daß es nur außerordentlich wenige gibt, für die das annähernd zutrifft. Ideal geeignet ist eigentlich keines. Nach der Meinung von *Stevenson* (1957) und *Becker* (1958) kann man annehmen, daß die geeigneten Merkmale auch

bisher schon zu Mutationsratenschätzungen herangezogen wurden. Wir möchten eher glauben, daß es außer den bisher für Mutationsratenschätzungen nach der direkten Methode verwendeten Merkmalen einige wenige gibt, die man noch zusätzlich heranziehen könnte. Viele sind es aber ganz gewiß nicht.

Auch unter den bisher verwendeten gibt es eine Reihe, die für die hier genannte Fragestellung nicht geeignet sind, obwohl man mit einer relativ hohen Mutationsrate rechnen muß, und obwohl es mit Hilfe der indirekten Methode möglich war, Werte zu errechnen, die aller Wahrscheinlichkeit nach wenigstens größenordnungsmäßig zutreffen dürften. Wir nennen etwa die Neurofibromatose, das Marfan-Syndrom, die dominant erbliche Form der Cystennieren, vielleicht auch die Dystrophia myotonica.

Für einige Merkmale, die uns einigermaßen geeignet erscheinen, ist in Tab. 2 die grob geschätzte Häufigkeit sporadischer Fälle zusammengestellt.

Hier findet sich auch ein X-chromosomal rezessives Merkmal, die frühe Beckengürtelform der Dystrophia musculorum progressiva. Wegen des frühen Erkrankungsalters, der Häufigkeit, der guten Diagnostizierbarkeit und des großen Selektionsnachteiles der Merkmalsträger halten wir diese Form trotz des Erbganges für geeignet. Man wird praktisch nur in relativ wenigen Fällen im Zweifel sein, ob man einen Fall als Neumutation an-

Tabelle 2

Ungefähre Häufigkeit von Neumutanten geeigneter Gene

Merkmal	Erbgang	Geschätzte Häufigkeit sporadischer Fälle	Autoren
Aniridie	Autos.-dom.	1:100 000	*Møllenbach*
Doppelseitiges Retinoblastom	Autos.-dom.	1:100 000	Häufigkeit aller sporadischen Fälle etwa 1:25 000, davon etwa ¼ doppelseitig
Chondrodysplasie	Autos.-dom.	1: 50 000	*Mørch; Stevenson*
Osteogenesis imperfecta tarda	Autos.-dom.	1: 50 000	Ganz grobe Schätzung auf Grund der Arbeit von *Seedorff*
Kindl. Beckengürtelform der Muskeldystrophie	χ – chromos.-rezessiv	1: 25 000 −1: 50 000	*Becker* und *Lenz*; *Walton*; *Stevenson*

sehen soll oder nicht. Außerdem besitzt dieses Merkmal eine Schlüssel-
position für die theoretisch so wichtige Frage, ob die spontane Mutations-
rate in den Keimzellen beider Geschlechter verschieden hoch ist.

Die Schätzungen beziehen sich bei dem doppelseitigen Retinoblastom
und der Muskeldystrophie auf die Geburtsjahrgänge, bei den übrigen
Merkmalen auf den Kopf der Bevölkerung. Wenn man Erhebungen über
mehrere Jahrzehnte hin durchführt, wird man die Mutationsrate ohnehin
immer durch Vergleich mit den Geburtsjahrgängen berechnen. Tut man
das nicht, dann kommt als weitere Fehlerquelle die verschiedene Lebens-
erwartung von Merkmalsträgern und Gesunden hinzu. Die Schätzungen
für die drei Merkmale Aniridie, Osteogenesis imperfecta tarda und Chondro-
dysplasie sind so grob, daß es nicht sinnvoll wäre, diesen Fehler hier zu
berücksichtigen, zumal unsere Berechnungen ja nur grob überschlags-
mäßigen Charakter haben.

Für die Neumutationen aller 5 Gene zusammen ergibt sich eine Häufigkeit
von $7,75-8/_{100\,000}$, also angenähert $^1/_{10\,000}$. Unter der sicher zu pessimistischen
Annahme, daß diese Gene allein für ausreichend genaue Mutationsraten-
schätzungen geeignet seien, hat man demnach etwa bei einer Bevölkerung
von 2,5 Millionen mit 250 Neumutanten zu rechnen, das heißt, bei zwei im
Abstand mehrerer Jahrzehnte ausgeführten Stichprobenerhebungen und
einem wirklichen Mutationsraten-Trend von 1,1 wäre der Erwartungswert

Tabelle 3

Bevölkerungsgröße und Genauigkeit der Erfassung von t. (t = 1,1)

Bevölkerungsgröße	Zahl der Neumutanten	$x_{1,2}$	Fehlerbereich	
			Obere Grenze	Untere Grenze
a) Pessimistische Annahme				
2,5 Millionen	250	525	1,2872	0,9128
5 Millionen	500	1 050	1,2324	0,9676
10 Millionen	1 000	2 100	1,1935	1,0065
50 Millionen	5 000	10 500	1,1418	1,0582
b) Optimistische Annahme				
2,5 Millionen	500	1 050	1,2324	0,9676
5 Millionen	1 000	2 100	1,1935	1,0065
10 Millionen	2 000	4 200	1,1660	1,0340
50 Millionen	10 000	21 000	1,1295	1,0705

für beide Stichproben zusammen $x_{1,2} = 525$. Bei $x_{1,2} = 525$ würde man diesen Trend mit $\pm 0,1872$ erfassen, was einer unteren Grenze von 0,9156 und einer oberen Grenze von 1,2872 entspräche. In Wirklichkeit lägen diese Fehlergrenzen sogar noch etwas weiter auseinander, da unsere Betrachtung von der Größe beider Stichproben zusammen ($x_{1,2}$) ausgeht, während man in Wirklichkeit zunächst nur die Größe der 1. Stichprobe kennt.

Für den gleichen Trend von 1,1 sind die Fehlerbereiche für einige Werte $x_{1,2}$ und die entsprechenden Bevölkerungsgrößen in Tabelle 3 zusammengefaßt.

Nun zu einigen konkreten Möglichkeiten der Planung einer derartigen Erhebung, die wir am Beispiel der Bundesrepublik Deutschland darstellen wollen.

Die Bundesrepublik (ohne Westberlin und Saarland) hatte am 13. September 1950 eine Bevölkerung von 47 695 700 Einwohnern. 1956 eine Bevölkerung von 50 595 400 Einwohnern. In den 10 Jahren von 1947 bis 1956 wurden im gleichen Bereich 7 749 668 Lebendgeborene registriert. Als Beispiel für einen kleineren Bereich greifen wir das Land Schleswig-Holstein heraus. Es hatte am 13. September 1950 2 271 000 Einwohner. Die Geburtenziffer betrug 1947–1956 380 748*.

Die Bevölkerungen beider Gebiete können als geeignete, wenn auch bezüglich der Geburtenziffern etwas pessimistische Modelle stationärer westeuropäischer Bevölkerungen betrachtet werden. Bei einer Häufigkeit der Neumutanten von $1/10\,000$ war in der Bundesrepublik im Laufe von 10 Jahren mit der Geburt von etwa 775 Neumutanten zu rechnen. Bei Annahme einer gleichbleibenden Geburtenziffer für die nächsten 10 Jahre und einem Trend $t = 1,1$ betrüge $x_{1,2} = 1628$. $|t' - t| = 0,1068$. Das heisst, die Vertrauensgrenzen für den Trend lägen gerade bei $\pm 0,1$. Nehmen wir optimischerweise an, es gelänge von Anfang an, durch Hinzuziehen neuer Merkmale Neumutanten in der Gesamthäufigkeit $1/5000$ zu erfassen, dann betrüge $x_{1,2} = 3256$: Ein Trend $t = 1,1$ ließe sich mit einer Genauigkeit von $\pm 0,075$ erfassen. Man würde die Genauigkeit vergrößern können, wenn man die vollständige Erfassung auf noch weiter zurückliegende Geburtsjahrgänge ausdehnen könnte.

Die gleichen Zahlen für das Land Schleswig-Holstein: Es sind innerhalb von 10 Jahren bei $1/10\,000$ 38 Neumutanten dieser Merkmale zu erwar-

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* Alle Angaben sind aus den Statistischen Jahrbüchern der Bundesrepublik entnommen. Die Geburtenziffern für 1956 sind vorläufige Zahlen, die aber in der Regel mit den endgültigen übereinstimmen.

ten. Das entspricht bei gleichbleibender Geburtenzahl in den nächsten 10 Jahren und einem Trend t — 1,1 einem Wert $x_{1,2} = 80$. Wegen der kleinen Zahl ist mit der Formel (7) nur eine grobe Abschätzung möglich. Es ergibt sich: für t — 1,1: $|t'-t| = 0{,}48$. Mit anderen Worten: Ich könnte einen Trend von 1,1 nur mit einer Genauigkeit $\pm 0{,}48$ abschätzen! Bei der Annahme einer Mutantenhäufigkeit $^1/_{5000}$ ergibt sich: $x_{1,2} = 160$, $|t'-t| = 0{,}339$. Mit anderen Worten: Der Trend 1,1 wäre nur mit etwa $\pm 0{,}34$ erfaßbar.

4. Diskussion

Die Planung von Untersuchungen über die Änderung der Mutationsraten muß von Vorstellungen darüber ausgehen, wie stark etwa die Mutationsrate schon angestiegen sein kann und in Zukunft etwa ansteigen dürfte. Nach den Vorstellungen, die man von diesem voraussichtlichen Anstieg hat, richtet sich der Anspruch an die Genauigkeit der zu ermittelnden Werte. Die extremste Annahme, die man machen kann, ist, daß die gesamte spontane Mutationsrate durch die Basisaktivität von rund 3 r hervorgerufen sei. Träfe diese Annahme zu, dann müßte eine Verdoppelung der ionisierenden Strahlung, wie sie in einigen Ländern vor allem auf Grund diagnostischer Röntgenstrahlen-Anwendung schon erreicht zu sein scheint (USA und Schweden; viel geringere Werte dagegen aus Großbritannien), auch die Mutationsrate verdoppeln. Man hätte also mit einem ganz erheblichen Mutationsraten-Trend zu rechnen. Dieser ganze Fragenkomplex ist sehr kompliziert, da noch zu wenig empirische Grundlagen für eine wirklich genaue Abschätzung vorhanden sind. Uns selbst erscheint nicht nur aus verschiedenen theoretischen Erwägungen heraus, sondern auch auf Grund der Befunde von *Neel* u. Mitarb. (1956) über die genetischen Effekte der Atombomben von Hiroshima und Nagasaki diese Hypothese äußerst unwahrscheinlich, während wir die Schätzung des Brit. Res. Counc. (1956), 5–20% der «spontanen» Mutabilität seien durch die Basisaktivität bedingt, für nach Lage der Dinge relativ wohlbegründet halten. Trifft sie zu, dann haben wir zum Beispiel bei Verdoppelung der uns treffenden Strahlendosis, wenn wir einmal alle anderen exogenen Mutationsursachen vernachlässigen, mit einem Mutationsraten-Trend von etwa 1,1 zu rechnen. Es ist nun Geschmackssache, mit welcher Genauigkeit man einen solchen Trend zu erfassen anstreben soll. Wir persönlich möchten aber doch glauben, daß derart kostspielige und auf lange Sicht geplante Untersuchungen nur dann begonnen werden sollten, wenn man Aussicht hat, einen Trend mit einer Genauigkeit von weniger als 0,1 $\pm$ zu erfassen. Was nützt es, derartige

Untersuchungen anzustellen, wenn auf Grund einfacher statistischer Betrachtungen sofort einzusehen ist, daß man selbst einen Trend von 1,1 oder höher überhaupt nicht mit einiger Sicherheit wird nachweisen können? Auf das konkrete Beispiel der Bundesrepublik bezogen heißt das:

Eine Erfassung der Bevölkerung des gesamten Bundesgebietes bietet die Aussicht, etwa einen Trend von 1,1 beim Vergleich, sagen wir, zweier Jahrzehnte mit der erforderlichen Genauigkeit zu erfassen, und zwar selbst dann gerade noch, wenn die sicher zu pessimistische Annahme zutreffen sollte, daß sich nur die oben in Tab. 2 aufgeführten Merkmale zur Mutationsratenschätzung mit der direkten Methode ausreichend eignen. Unter der optimistischen Annahme, daß die doppelte Anzahl von Neumutanten erfaßt werden kann, ergibt sich schon ein relativ befriedigendes Resultat. Es kann noch genauer gestaltet werden, wenn es gelingt, die Zahl der ausreichend vollständig durchuntersuchten Geburtsjahrgänge zu vermehren.

Dagegen gestattet die Untersuchung einer kleineren Bevölkerung von 2–3 Millionen, wie sie etwa das Land Schleswig-Holstein besitzt, bei weitem keine ausreichend genaue Abschätzung eines Mutationsraten-Trends, wenn wir einmal von ganz extremen und unwahrscheinlichen Größenordnungen absehen. Ein ausreichendes Ergebnis ist, wenn überhaupt, dann nur nach viele, viele Jahrzehnte umfassenden Erhebungen (etwa Vergleich zweier 50-Jahres-Gruppen) zu erwarten.

Das statistische Argument für eine möglichst groß angelegte Erhebung wird noch verstärkt durch die Tatsache, daß die genannte statistische Ungenauigkeit nur die eine Seite des Problems ist. Mindestens genau so groß sind die Ungenauigkeiten, mit denen man bei der Materialerfassung selbst rechnen muß. Wird es tatsächlich gelingen, alle Merkmalsträger zu erfassen? Ist in jedem sporadischen Fall die Diagnose sicher zu stellen? Verwirren Phänokopien das Bild? Diese und alle anderen Fehlerquellen lassen das ganze Unterfangen auf den ersten Blick fast utopisch erscheinen. Es gehört schon ein hohes Maß an Optimismus dazu, überhaupt ein derartiges auf lange Sicht geplantes Unternehmen zu beginnen. Eine gewisse Berechtigung hat ein solcher Optimismus aus der Erwägung heraus, daß die Bearbeiter im Laufe ihrer Erhebungen die ausgewählten Merkmale immer genauer kennen lernen werden, was sie in die Lage versetzen wird, die Fehlerquellen bei der Materialerfassung mehr und mehr zu verkleinern.

Eine weitere Fehlerquelle liegt in der Frage: Sind die ausgewählten Testmutationen in bezug auf die Strahlenempfindlichkeit für das Gesamtgenom repräsentativ? Bei Mikroorganismen gibt es im Verhältnis Spontanmutabilität/strahleninduzierte Mutabilität durchaus Unterschiede zwischen einzelnen Loci (*Friedrich-Freksa*, Disk.-Bem. zu *Loeffler* 1957).

Diesen möglichen Fehler kann man möglichst klein halten, indem man die Zahl der untersuchten Loci nach Möglichkeit etwas (vielleicht auf etwa 10–12) vergrößert. Wir sagten schon, daß sich zusätzlich zu den genannten sicher noch einige weitere als geeignet erweisen werden.

Zusammenfassung

Es wird untersucht, mit welcher Genauigkeit sich eine Steigerung der spontanen Mutationsrate beim Menschen in der Zeit in Abhängigkeit von der Stichprobengröße zweier in einigem Abstand durchgeführter Erhebungen erfassen läßt. Bei dieser Gelegenheit wird ein mathematisches Modell angegeben, mit dessen Hilfe es möglich ist, die Fehler- und Vertrauensgrenzen eines Trends zwischen zwei Stichproben zu errechnen. Bei Anwendung auf das Mutationsproblem ergibt sich: Unter westeuropäischen Bedingungen kann man mit ausreichend genauen Ziffern rechnen, wenn man seine Erhebungen bei einer Bevölkerung von etwa 50 Millionen durchführt. Für sehr wesentlich kleinere Bevölkerungen ist dagegen mit einem ausreichend genauen Ergebnis – abgesehen von anderen Fehlerquellen – schon aus statistischen Gründen nicht zu rechnen.

Summary

The possibilities of evaluating the trend in time of the spontaneous mutation rate in man are discussed. The authors analyse the relation between the precision of an estimate of this trend and the size of the population under consideration. By use of a mathematical model they find that a population of 50 millions may be expected to give a satisfactory precision under the conditions prevailing in Western Europe.

Résumé

Les auteurs discutent l'exactitude avec laquelle on peut évaluer une augmentation de la fréquence spontanée de mutation chez l'homme en relation avec le temps écoulé entre l'estimation des valeurs d'échantillonnages obtenues. A cette occasion ils exposent un modèle mathématique grâce auquel il est possible de calculer les erreurs et les limites fiduciaires en comparant deux échantillonnages. En l'appliquant au problème de la mu-

tation, on trouve le résultat suivant: d'après les conditions qui existent dans l'Europe de l'Ouest, on obtient des chiffres suffisamment exacts si l'on se base sur les constatations faites chez environ 50 millions d'habitants. Pour une population plus petite, il ne faut pas s'attendre à un résultat exact du point de vue statistique et cela d'autant moins que d'autres causes d'erreurs entrent en ligne de compte.

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A CATAMNESTIC INVESTIGATION OF DANISH TWINS*)

A survey of 3100 pairs

By B. HARVALD and M. HAUGE

During the last decades it has been repeatedly emphasized that the conquest of infectious diseases and starvation implies a constant increase in the importance of heritable disorders for the morbidity and mortality in modern society. Similarly, inborn, gene-determined traits will influence the course of life of the individual in health and disease to an even greater extent.

Examination of an extensive and representative twin series opens the possibility of evaluating the role played by heredity where life-shortening and disabling factors in a population are concerned. The majority of twin studies, however, were based on twin probands selected from samples of patients with specific diseases. This implies the considerable risk that too many concordant, monozygotic pairs are included with consequent over-estimation of the genetic factors. With the object of overcoming these difficulties, a study of a complete Danish twin population from a 40-year period was commenced four years ago.

Material

The project was planned as a catamnestic investigation of all twins born in Denmark in the years 1870–1910. The study profits by the acces-

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sibility of information concerning all births in this country, of case records from all Danish hospitals, both public and private, and from the general practitioners, and finally of death certificates, which permits a follow-up of the individuals in this population.

Our basic project is, at present, half completed and a brief report of the results obtained hitherto is considered to be of value.

The present composition of the material is shown in Table 1. The very

Table 1

Survey of the Material. State on March 1, 1958

Total number of pairs registered	*11 900*
Number of pairs examined	3 100
Pairs excluded on account of the death of one or both partners before the age of 5 years	4 500
Pairs not yet traced	4 300

high death rate among infants, especially before the end of the last century. is, in a sinister way, reflected in the remarkable number of twin pairs broken by death in early years. These pairs, where one or both partners died before the age of five, were excluded from further consideration. As the study is still in progress the number of twins not yet traced is rather high; the final loss of pairs cannot yet be estimated.

Results

The most important results are shown in Tables 2–9. The twin pairs have been arranged in three groups: 1. monozygous twin pairs, 2. same-sexed diszygous twins and 3. twin pairs of different sex. Within each group the number of concordant and discordant pairs is indicated. Discordant pairs are only included if the co-twin has survived a reasonable period of observation in order to avoid the source of error caused by pairs in which the co-twins died at an early age, in which case only very limited information is gained. In cardio-vascular diseases, for instance, only those pairs have been included in which the healthy co-twin has reached the age of at least 60 years.

In calculating the concordance rate the way of collecting the material must be borne in mind. Concordant pairs must appear twice because both twins are probands in this study of an unselected twin sample.

Cardiovascular disorders and malignant growths are numerically superior causes of death in the Danish population. These groups will consequently be considered first.

Table 2

Cardiovascular Disorders in Twins

| | Coronary Occlusion (82 Pairs > 60 Years) | | | Cerebral Apoplexy (86 Pairs > 60 Years) | | |
| | 17 MZ Pairs | 65 DZ Pairs | | 21 MZ Pairs | 65 DZ Pairs | |
		Same Sex	Diff. Sex		Same Sex	Diff. Sex
Concordant	1	2	2	5	3	0
Discordant	16	32	29	16	21	41

In coronary occlusion, the concordance rate is of the same magnitude in all three groups (Table 2). This indicates that genetic factors, generally speaking, play only a minor role in the etiology of coronary arteriosclerosis. The well-known type of coronary sclerosis based on familial hypercholesterolaemia is evidently too rare to influence these results. On the other hand, it appears that the rate of concordance in cerebral apoplexy is higher in monozygous pairs than in dizygous. This suggests that some of the etiological factors may be genetically determined, probably hypertension as suggested by previous studies.

All types of malignant growths are summarized in Table 3, which

Table 3

Malignant Growths in Twins
(345 Pairs > 40 Years)

| | 74 MZ Pairs | 271 DZ Pairs | |
		Same Sex	Diff. Sex
Concordant	7 (3)	5 (2)	10 (2)
Discordant	67	120	136

The figures in brackets () indicate the number of pairs also concordant as regards the site of the tumour.

includes 345 twin pairs all of whom have survived the age of 40. A distinction was drawn between concordance as far as cancer in general is concerned and concordance of site of the tumour. Although a significant difference between the monozygous and the same-sexed dizygous groups is found, the low rate of concordance is striking. It seems reasonable to investigate more details when searching for hereditary factors in cancer as special conditions may apply to the various groups. However, our material is still limited when the individual types are considered (Table 4), but the figures suggest that genetic factors may be more significant in cancer of the breast, colon and rectum. In addition, it is our impression that concordance is more frequently found in rather benign types of cancer than in the groups of high malignancy.

Table 4

Malignant Growths in Twins

Primary Site	MZ Pairs	DZ Pairs	
		Same Sex	Diff. Sex
Stomach (57 Pairs)			
Concordant	1 (0)	2 (0)	2 (2)
Discordant	14	22	16
Colon-Rectum (45 Pairs)			
Concordant	2 (2)	3 (1)	1 (0)
Discordant	11	14	14
Breast (49 Pairs)			
Concordant	2 (1)	1 (1)	2 (0)
Discordant	7	13	24
Uterus (28 Pairs)			
Concordant	0	1 (0)	2 (0)
Discordant	3	10	12

The figures in brackets () indicate the number of pairs also concordant as regards the site of the tumour.

It thus appears that diseases causing the majority of deaths in modern society are only influenced by hereditary factors to a very limited extent. However, it may also be of interest to consider some of the common disabilities, which are not directly fatal, but where the complications

nevertheless may involve a considerable shortening of the life of the individual concerned. In agreement with German twin series published previously and with numerous proband studies on heredity in diabetes our results suggest a considerable hereditary factor. but our material (Table 5) is still too limited to permit any decision as to whether heredity plays a role in juvenile diabetes only.

Table 5

Diabetes Mellitus in Twins

(82 Pairs > 40 Years)

| | 16 MZ Pairs | 66 DZ Pairs | |
		Same Sex	Diff. Sex
Concordant	5	1	1
Discordant	11	34	30

Among allergic diseases, reliable figures were only obtained for bronchial asthma. As anticipated, we found a considerable number of concordant cases among monozygous twin pairs (Table 6). A sufficiently thorough examination of these pairs. however, has not yet been undertaken; perhaps the number of concordant pairs will prove to be still higher than our figures, which represent a minimum.

Table 6

Bronchial Asthma in Twins

(97 Pairs > 40 Years)

| | 25 MZ Pairs | 72 DZ Pairs | |
		Same Sex	Diff. Sex
Concordant	9	2	3
Discordant	16	33	34

The same applies to peptic ulcer (Table 7). In the group of concordant pairs only such pairs are included in which both co-twins have been hospitalized on account of ulcer. One of our co-workers, however, is at present undertaking a thorough examination of all ulcer pairs including X-ray of the stomach and duodenum in all living individuals, and it is probable that a higher concordance rate will appear when the examination is complete.

Table 7

Peptic Ulcer in Twins

(181 Pairs > 40 Years)

| | 44 MZ Pairs | 137 DZ Pairs | |
		Same Sex	Diff. Sex
Concordant	8	8	2
Discordant	36	54	73

Table 8

Graves' Disease in Twins

(88 Pairs > 40 Years)

| | 24 MZ Pairs | 64 DZ Pairs | |
		Same Sex	Diff. Sex
Concordant	11	1	1
Discordant	13	28	34

In Graves' disease, genetic factors apparently play an important etiological role as shown in Table 8.

Finally, the cases of major psychoses in the twin population are summarized in Table 9. Although our material is still limited it seems to be in

agreement with the more extensive investigations carried out in U.S.A. and England in recent years.

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Table 9

Psychoses in Twins

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	Schizophrenia			Manic-depressive Psychosis		
	(34 Pairs > 40 Years)			(23 Pairs > 40 Years)		
	5 MZ Pairs	29 DZ Pairs		7 MZ Pairs	16 DZ Pairs	
		Same Sex	Diff. Sex		Same Sex	Diff. Sex
Concordant	3	1	1	4	1	0
Discordant	2	15	12	3	7	8

In concluding this survey covering a few selected diseases, the study of longevity in twins would sum up the influence of heredity on the total load of life-shortening disabilities. This particular study is in progress at present, but we have not yet succeeded in finding a satisfactory method of estimating the relative importance of heredity and environment in longevity. In twin pairs, in which both partners have died by the time of examination, we have found the interval between the deaths of the co-twins significally shorter in monozygous than in dizygous pairs.

As stated above, the results published here are only preliminary. On one hand, our registration of all twins from the 40-year period is not yet complete, and on the other hand the thorough study of individual traits has just commenced as the material has attained a reasonable size. In this latter respect, our attention is particularly directed towards the monozygous, discordant pairs. They open an outstanding opportunity to analyze the effect of differences in environmental stress on identical genotypes. In this way the authors hope to extend the scope of the twin investigation and to amplify the design from being strictly genetic to comprise the study of etiology and pathogenesis in general.

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Summary

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A brief survey is given of the preliminary findings in a study of an unselected series comprising all Danish twins born in the period 1870–1910.

Zusammenfassung

Es wird ein kurzer Überblick über die vorläufigen Ergebnisse einer Untersuchung an einer unausgelesenen Serie aller von 1870 bis 1910 geborenen dänischen Zwillinge gegeben.

Résumé

Les auteurs donnent un aperçu préliminaire sur les constatations qu'ils ont pu faire lors de l'examen d'une série non sélectionnée de tous les jumeaux nés au Danemark entre 1870 et 1910.

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FIRST-COUSIN MARRIAGES IN SWEDEN 1750–1844 AND A STUDY OF THE POPULATION MOVEMENT IN SOME SWEDISH SUBPOPULATIONS FROM THE GENETIC-STATISTICAL VIEWPOINT

A Preliminary Report

By CARL HENRY ALSTRÖM

Translated from the Swedish by Erica Odelberg

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PREFACE AND INTRODUCTION

The investigation of which this is a preliminary report was started in the spring of 1956. It is partly a complement to a more extensive investigation of schizophrenia and manic-depressive disorders in the county of Östergötland, situated in the south-central part of Sweden. Together with my colleagues, Drs. *Kj. Fastborg* and *D. Kay*, I am engaged in studying there the frequency, clinical course and heredity of the aforementioned diseases. According to some Swedish investigators *(T. Sjögren, J. A. Böök)*, it seems reasonable to assume that both the frequency and the clinical features may vary somewhat in different parts of the country.

In view of the possible occurrence of such differences, it seems desirable and valuable, from the genetic-psychiatric point of view, to try to obtain an idea of the population-genetic background in the region in question. For comparison, it is important to investigate samples from various parts of the country.

For this purpose, the population must be studied for several generations back, with respect to the existence of eventual isolate formations and their changes, as well as any geographic variations in population structure from a genetic-statistical viewpoint.

Sweden is presumably the only country in the world to possess an unbroken series of official population statistics dating as far back as the middle of the 18th century. The parish registers, kept in the archives, contain exceedingly valuable material concerning the population movement, going back to a still earlier date. The chief line followed in this investigation is to study, on the basis of this empirical material, small population samples i.e., parishes – the smallest administrative units – with regard to the marriages contracted within them. The marriage partners are identified with respect to such factors as their own birthplaces and those of their children, if any, the number of these children, as well as the number reaching adult age and marrying, and their place of marriage. In certain samples, several generations will be followed up.

An attempt is also made to apply to these data the approach developed by *S. Wright*, for investigation of isolation factors. To cite *Morton*, this

approach seems to be much richer in genetic applications than are other methods developed, for instance, on the basis of first-cousin marriage frequencies. Here, I have, however, attempted to use such data in estimating "isolate" sizes as well.

Although the attempts that have been made to follow these lines may appear defective and tentative, they may perhaps give a very rough idea of the phenomena studied. Consequently, it seems justified to present them, even if only in a preliminary form, in view of the fact that they deal with actually existing empirical conditions in a unique material.

Stockholm, November 1958. *Carl Henry Alström*

I. THE QUESTION OF NON-RANDOMNESS IN CONSANGUINEOUS MARRIAGE

In 1929 and later, *Dahlberg* elaborated a method for calculating the size of "genetic isolates" in human populations, based on the frequency of first-cousin marriages. The calculation presupposes that, in panmixia, marriages between relatives occur at random. The frequency of such marriages will then depend on the family size, and on the size of the sub-population or the "isolate" within which the marriages occur.

In each family, the average number of children who reach adult age and marry is denoted by b, and the number of persons within the isolate by n. Such a person mating at random has $b(b\text{-}1)$ first cousins with whom he/she can mate, and the total number of individuals with whom he/she can mate is $\dfrac{n}{2}$. The probability of such marriages is denoted by c; $c = \dfrac{2\,b\,(b\text{-}1)}{n}$ and $n = \dfrac{2\,b\,(b\text{-}1)}{c}$ (see further *Dahlberg* 1943, p. 115).

Since Western populations, e.g. the population of Sweden, are nowadays on the whole constant under "ordinary" conditions, it can be presumed that, in each marriage, an average two children reach adult age and marry. *Dahlberg* pointed out that, with the assumption of an average three such children per marriage, the population would increase by 50 per cent from one generation to the next. If the frequency of first-cousin marriages is known, it should be possible to calculate the size of the isolate. With these premises, *Dahlberg*'s arguments seem fairly reasonable.

Formulas for other types of consanguineous marriage can be derived in the same way, as *Dahlberg* has discussed. *Morton* (1955) has taken up this problem, and has shown how there are great discrepancies in the estimates of isolate size from different types of consanguineous mating, such as uncle-niece and aunt-nephew, first cousins, first cousins once removed, and second cousins. *Morton* stated that it is doubtful whether such estimates are reliable or useful measures of population structure. Table 2 in his paper, illustrating this statement, makes *Morton*'s pessimism understandable.

There are chiefly two sources of error inherent in the data on which such calculations are based. The first is that consanguineous matings do *not* occur at random. The second is that the collected data are incomplete. The first is particularly true of uncle-niece and aunt-nephew matings, against which there is a strong prejudice in western countries, this also being reflected in the legislation. In addition to this "incestuous" prejudice, a more general one exists, in view of the large age difference between two consecutive generations. Obviously, this prejudice is greater when the woman belongs to the older generation than when the reverse applies. But the frequency of the latter type of mating is also far less than at random, even among unrelated persons.

The age difference factor – between two generations, for instance – must, in fact, be taken into account as an isolation barrier, in the same way as social or geographic differences, and may perhaps be an even stronger one.

We must agree with *Morton* that data on uncle-niece and aunt-nephew matings are completely useless as a measure of population structure.

A more reasonable hypothesis is that marriages between more distant relatives than first cousins, e. g. second cousins and so on, occur at random. Owing to the difficulty of collecting such data, they are, as a rule, far from complete. This can be confirmed even by slight experience of genealogical work, which is a necessity for checking data obtained only by inquiries. Well-kept, accurate parish registers and civil registers are a *sine qua non* for such investigations. We must, however, agree with *Morton* that official data regarding this type of consanguineous marriage are unreliable as a measure of population structure.

The question of first-cousin marriages then arises. Naturally, data obtained by mere inquiries are more reliable in this case than when remoter relationships are concerned. But these data as well must be checked through the parish registers, even if this results in only relatively small corrections. Although the necessary genealogical checking is an extensive procedure, it is nevertheless practicable. This is, on the contrary, scarcely applicable to control of data regarding more remote relationships, such as second-cousin matings, and so on.

The main source of error in using data of first-cousin marriages as a measure of isolate size does not, however, seem to be eventual incompleteness of the data. It is rather that such matings may not occur at random. If, as in Japan, first-cousin marriages are highly favoured *(Neel et al., Shull et al.)*, their frequency is not useful as a measure of isolate size, since it gives too low estimates. Errors in the opposite direction, i. e., too high estimates, can be made in typical immigrant countries with unstable populat-

ions. Immigrants are single persons, or at most single families, removed from their "natural" populations. They have fewer cousins, or none at all, with whom they can mate in the new country, until two or three generations have passed. This may provide one explanation of the very low frequency of first-cousin marriages – 0.05 per cent – among white private obstetrical cases in Baltimore, reported by *Glass* (1954).

It has been assumed that the frequency of consanguineous marriages has greatly declined in Western Europe during the past two centuries (e.g. *Dahlberg* 1929, 1943, *Glass* 1954). This may be true for Prussia and Bavaria, which are often mentioned as examples. In these states, the frequency of first-cousin marriages fell from 0.71 and 0.87 per cent, respectively, in 1875–1880 to 0.2 per cent in both states in 1921–1926.

There are, however, many other reports from European countries which do not show any great decline in the frequency of first-cousin marriages. On the contrary, in some large cities in which low figures could be expected, for example, London, Vienna and Copenhagen, the frequency recorded in recent years was 0.61–0.40, 0.68–0.53 and 1.2 per cent, respectively. In France, the frequency in 1939 was 0.97 per cent, namely, about the same as 50 years earlier. It may be of interest to note that, although London and Vienna are cities of over millions people, their resident population has been relatively stable. Thus, at the end of the 19th century, 62.9 per cent of the population of London was born in the city, the figure for 1921 being 69 per cent. The corresponding figures for Vienna are 34.5 and 54 per cent, respectively. In Vienna, the percentage of those born in the city has thus increased (*Sorokin* 1927, *Thörnberg* 1935) during a period when the frequency of first-cousin marriages showed a decrease from 1.02 to 0.74 per cent. The actual decrease occurred, however, during the years 1913–1930, from 0.99 to 0.74 per cent (*Orel* 1932).

Dahlberg, in an Addendum to his paper of 1938, mentions the average figures for Italy during two periods, showing "a decrease in the frequency of first cousin marriages from 0.77 per cent, 1868–1870, to 0.44 per cent, 1931–1935". It can be inferred from the figures discussed on page 314 of the present paper that a minimum was reached as early as around 1918–1920. Since then, the curve has, in fact, shown a steady increase, and the figure 0.44 per cent occurred during this period. In 1952, the frequency of first-cousin marriages in Italy amounted to 0.48 per cent.

It seems probable that when a decrease in first-cousin marriages has occurred in Western European countries, it has been almost entirely confined to the past 50 years. It does *not* appear – or is not proved – to have been a process extending over the past two centuries, at any rate in

the population as a whole, although it may perhaps apply in some small social groups, e.g. the nobility.

The question is, in fact, whether – with respect to the increase and particularly the breaking up of the "isolates" – the change in the population structure in European countries has actually been *so* far-reaching during the past centuries up to World War II as has hitherto been postulated. As far as Sweden is concerned, neither the frequency figures for first-cousin marriages nor for migration, of which an account will be given in the following, lend support to such an assumption. In order to elucidate this question, it is necessary to collect and have available more statistical material from former times than is now the case.

In this respect, Sweden is particularly fortunate, since an unbroken annual series of population-statistical data exists ever since 1749, and the parish registers go back to a still earlier date.

II. FIRST-COUSIN MARRIAGES IN SWEDEN 1750–1844

Western civilized societies have not differed essentially from so-called primitive or native societies with respect to the development of taboos against marriage between relatives. This seems to be a universal phenomenon and, in principle, it is as difficult from a logical point of view to understand the taboos of the Catholic Church, for instance, as those of many Australian tribes. The true reasons underlying them are obviously as deeply buried and as unconscious in both cases, and their innermost nature is amenable only to psychologic research.

For almost 1,000 years, the Catholic Church forbid marriage between persons related up to the seventh degree, this prohibition being originally based on the fact that the world was created in seven days. When this precept was no longer tenable, the number of forbidden degrees was reduced to four. These were "chosen" in view of the four elements, namely, earth, water, air and fire. (See also *Almquist*'s (1953) interesting analysis.) This prohibition, as well as the celibacy of the clergy, which was also strictly enforced by the Catholic Church at that time, must be seen against the general attitude of this Church to sexual matters.

In those countries in which the Reformation made advances, Catholic or canon law was set aside, and was replaced by corresponding precepts regarding forbidden degrees of relationship in the Bible, according to the law of Moses. In this law, marriages between first cousins did not belong to the forbidden degrees. A steadily increasing frequency of first-cousin marriages in these countries, where it had formerly been about zero, can then be assumed to have occurred since the 16th century. Strangely enough, Sweden was an exception. Here, the precepts of canon law were retained on this point. The historical development in this respect presents many interesting psychological aspects, which space does not permit entering into here. It suffices to note that the Swedish Church managed to enforce a strong prohibition against first-cousin marriages, for which not even a dispensation was granted, as long as to the year 1680. A Royal decree then made it possible for first cousins wishing to marry to seek a dispensation from the King in Council.

This did not, however, mean that ecclesiastical resistance was broken, and the right to a dispensation was only very seldom exploited. Occasional dispensations were granted at intervals of several years, and during certain periods none at all were granted. During the first half of the 18th century – after the reign of Charles XII, which ended in 1718 – the restrictions seem to have become slightly relaxed. This did not, however, prevent a Royal decree of 1725 stating that cousins who had had sexual relations should, as being unworthy, be denied the right of marrying each other. According to *Almquist* (1953) this was no longer enforced in the latter half of the century.

From the beginning of the 19th century, attempts were made at several sessions of the Riksdag, particularly those of 1809, 1823 and 1829, to remove the prohibition against marriage for first cousins, but without results. This was not successful until 1844.

All the dispensations granted from 1750–1844 were registered, and these records have been kept in the National Archives (Riksarkivet) in Stockholm. I have made an analysis of this material. Thanks to the organization of Swedish population statistics, and establishment of the precursors of the Central Bureau of Statistics, Tabellverket in 1749 and Tabellkommissionen in 1756 (See *Hjelt* 1900), it is possible to obtain an exact picture of the development of the frequency of first-cousin marriages in Sweden during the 1750–1844 period. A numerical presentation is given in Table 1.

Before starting to discuss the table, the facts can be summarized as follows. During about 600–700 years, the frequency of first-cousin marriages in Sweden may be judged as practically zero; this applied to all classes of society. During the first half of the 18th century, a change seems to have take place, despite strong resistance by the clergy; the incidence of first-cousin marriages rose, and by 1750 had reached 2 in 1,000 (see Table 1).

During the next few decades, the frequency of first-cousin marriages remained relatively stable at about 3 to 4 in 1,000. This was followed by a slow rise to about 1 per cent around 1800. It then remained on this level until the end of 1829.

The rise during the 1750–1829 period was thus, with small random variations from year to year, extremely slow and continuous.

From 1829 to 1830, an abrupt, statistically significant increase occurred from 1.0 to 1.3 per cent, and the frequency subsequently remained at about 1.5 per cent until 1844. The series is then terminated, since a dispensation for marriage between first cousins was no longer necessary after this year.

It is evident from a study of the reports of parliamentary proceedings (riksdagsprotokollen) of 1809–1810, 1823, 1829 and 1844 that the clerical

Table 1. Frequency of first-cousin marriages in per cent of all marriages contracted
in Sweden 1750–1844

Year	%	Year	%	Year	%	Year	%
1750	0.2	1774	0.5	1798	1.0	1822	1.1
1751	0.4	1775	0.4	1799	0.9	1823	1.0
1752	0.4	1776	0.5	1800	0.8	1824	1.0
1753	0.3	1777	0.4	1801	0.8	1825	1.0
1754	0.3	1778	0.5	1802	1.1	1826	1.0
1755	0.3	1779	0.5	1803	0.9	1827	0.9
1756	0.3	1780	0.6	1804	0.9	1828	1.0
1757	0.3	1781	0.6	1805	0.7	1829	1.0
1758	0.3	1782	0.4	1806	1.0	1830	1.3
1759	0.3	1783	0.5	1807	1.0	1831	1.5
1760	0.3	1784	0.7	1808	1.1	1832	1.4
1761	0.3	1785	0.7	1809	0.8	1833	1.4
1762	0.3	1786	0.6	1810	0.9	1834	1.3
1763	0.4	1787	0.8	1811	0.9	1835	1.5
1764	0.3	1788	0.7	1812	1.0	1836	1.6
1765	0.4	1789	0.6	1813	1.0	1837	1.5
1766	0.4	1790	0.7	1814	1.2	1838	1.5
1767	0.4	1791	0.7	1815	1.1	1839	1.4
1768	0.4	1792	0.7	1816	1.1	1840	1.6
1769	0.3	1793	0.6	1817	1.1	1841	1.5
1770	0.5	1794	0.7	1818	1.2	1842	1.4
1771	0.4	1795	0.8	1819	1.2	1843	1.4
1772	0.3	1796	0.8	1820	1.1	1844	1.5
1773	0.5	1797	0.9	1821	1.2		

resistance to first-cousin marriages – this curious tradition in Swedish theology, differing from that of Protestant churches on the Continent – was in principle the same as earlier. But it had a decreasing response in the population. And, during the early part of the 19th century, the main factor counteracting such marriages seems unquestionably to have been an economical one. Application for a dispensation was not only troublesome formally, but was associated with a considerable outlay, both to the Crown and to the commissioners who acted as intermediaries, and who remunerated themselves at the expense of the applicants. It is clearly evident that, actually, only wealthy persons could afford it. The reports of parliamentary proceedings in 1829 show that the costs amounted to 8–10 riksdaler banco which, at that time, represented the entire cash

earnings of a farm labourer or day labourer for several months, often half a year (see e.g. *Utterström* 1956).

This offensive economical barrier was removed altogether at the 1829 Riksdag, at the same time as the actual application for a dispensation was greatly simplified. This is the probable cause of the abrupt rise in the frequency from the 1 to the 1.5 per cent level. The latter seems to be the "natural" level for the frequency of first-cousin marriages, to which the population rapidly became adapted. Taking into account that, during that century, the population of Sweden increased by 30–40 per cent in each generation, the average "isolate" size in this country about 100 years ago should be 400–450 individuals, calculated with *Dahlberg*'s formula given on page 298.

In 1830–1844, the applications were not sent directly to the King in Council, as before, but were collected in each diocese. With the help of this material, kept in the National Archives, it was possible to obtain the figures for the first-cousin marriages in different parts of Sweden. The figures for the three 5-year periods 1830–1834, 1835–1839 and 1840–1844, listed from the north of Sweden to the south, are given in Table 2. The districts (dioceses) are shown in Fig. 1.

We can now consider the 1840–1844 period in Table 2. It is interesting to note that, if the island of Gotland in the Baltic is disregarded, the highest frequency of first-cousin marriages, 2.5 per cent, is found in the north. Frequencies of the same order of magnitude, 2.1 per cent, are found in the west of the country, in districts 4 and 5. The northwest part of district (Diocese) 3 is the county of Dalarna. In this county, situated between districts 1 and 4, the frequency of first-cousin marriages is 1.8 per cent, whereas in the south-eastern part of district 3 the corresponding figure is 1 per cent, lower than the average for the country as a whole, and in agreement with the figure for the central eastern part of the country.

Remarkably enough, the next in order, with 1.7 per cent, is the county of Skåne of district 12 in the south, the most densely populated part of the country. The western part of this district has a higher frequency than the eastern part.

The lowest frequencies, 0.8, 1.0 and 0.7 per cent, are noted in the central and eastern parts of the country, i.e., districts 7, 9 and 11, respectively. The lowest frequency, 0.7 per cent, is found in the capital, Stockholm, on the east coast. The figures for the intermediate districts 6 and 10 are 1.0 and 1.2 per cent, respectively.

It seems as if there is a more or less *continuous* decrease in first-cousin marriages from the northern, western and southern parts of the country

Table 2. Frequency of first-cousin marriages in 5-year periods, 1830–1844, in different districts (Dioceses) of Sweden, listed from north to south.

District (Diocese)	1830–1834			1835–1839			1840–1844		
	first-cousin marriages	total no. of marriages	%	first-cousin marriages	total no. of marriages	%	first-cousin marriages	total no. of marriages	%
1. Härnösand	143	7,268	2.0	152	7,496	2.0	223	8,976	2.5
2. Uppsala	130	11,659	1.1	141	10,705	1.3	137	11,169	1.2[1]
3. Västerås a) Dalarna							102	5,590	1.8
3. Västerås	115	8,835	1.3	125	8,436	1.5			
b) Västman-land							38	3,960	1.0
4. Karlstad	192	8,991	2.1	188	8,370	2.2	202	9,601	2.1
5. Göteborg	204	10,905	1.9	243	10,967	2.2	248	11,861	2.1
6. Skara	115	8,801	1.3	124	8,609	1.4	97	9,574	1.0
7. Strängnäs	63	7,957	0.8	70	7,512	0.9	67	7,907	0.8
8. Stockholm	19	3,166	0.6	19	3,317	0.6	21	3,114	0.7
9. Linköping	104	11,963	0.9	82	11,123	0.7	112	11,638	1.0
10. Växjö	91	7,761	1.2	82	7,377	1.1	97	8,018	1.2
11. Kalmar	41	4,126	1.0	37	4,028	0.9	32	4,267	0.7
12. Lund a) Skåne							238	14,020	1.7
12. Lund	235	16,872	1.4	280	15,953	1.8			
b) Blekinge							43	3,550	1.2
13. Visby	34	1,568	2.2	32	1,346	2.4	39	1,489	2.6
The whole country	1,486	109,872	1.4	1,575	105,239	1.5	1,696	114,741	1.5

[1] After completing the table, figures have become available for the north and south part seperately of Diocese 2 (see Fig. 1), i.e. 2.0 and 0.7 per cent respectively for the period 1840–1844.

to the central and eastern parts. This is illustrated in Figure 2. in which the frequencies in the different districts in 1840–1844 are plotted highly schematically.

This differentiation seems to be of added interest in that it is, to some extent, in agreement with the demographic differences between western and eastern Sweden found by *Sundberg* (1910), *Flodström* (1915) and, more recently, by *Bergsten* (1951). In the present connexion, the most important feature is that the fertility of the marriages was greatest in western Sweden, with a falling frequency towards the eastern part. According to *Flodström*, this difference can be demonstrated up to the middle of the 18th century, to the beginning of our official population statistics.

Fig. 1.

Map of dioceses (*cf.* Tables 2 and 3)

Fig. 2

Schematic geographic distribution of frequency of first-cousin marriages In Sweden 1840–1844. See further text.

——— the latitude of Stockholm.
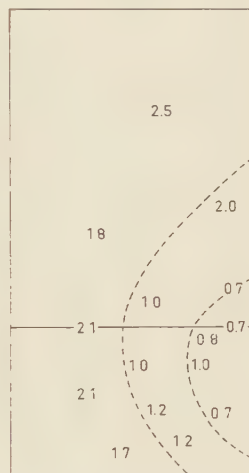
In all three consecutive 5-year periods, the same geographic differences can be noted, with relatively constant figures of the same order of magnitude in each district. In Appendix 2, this can also be seen to apply, year by year, during the six years 1839–1844. There may possibly be an increasing trend in the north, so that it is not until the latter part of the 19th century that the population there becomes adapted to a more "natural" and constant level, above 2.5 per cent.

III. GEOGRAPHIC DISTRIBUTION OF FIRST-COUSIN
MARRIAGES IN SWEDEN 1839–1844; POPULATION DEN-
SITY, AND ISOLATE SIZE ACCORDING TO DAHLBERG'S
FORMULA. TREND OF FIRST-COUSIN MARRIAGES IN
ITALY IN RECENT TIMES.

Table 3 must first be described. In column (1) the *land* area is given
in square miles[1]. The northernmost district, D.1, Härnösand (D = Diocese),
differs essentially – both in size and sparsity of population – from the rest
of the country. At that time, half of it, i.e., Lapland, was practically waste
land. In the following calculations, it seems most reasonable to take into
account only the populated half. For comparison, figures for the whole
district are given in brackets.

Column (2) gives the average number of marriages contracted per
square mile (100 km²) during the 6-year period 1839–1844, and column (3)
the frequency of first-cousin marriages as a percentage of all marriages
during this period. Using the figures in column (3), the "isolate" size has
been calculated with *Dahlberg*'s formula given on page 298; these figures
are listed in column (4). Column (5) shows the average number of inha-
bitants per square mile in the different parts of the country in 1840. The
average figure for the whole country, 1.030, has been calculated with the
exclusion of half the D.1 district, discussed above, and the population of
Stockholm, the capital. The bracketed figures have been calculated with-
out these exclusions.

It is important to recall that, at this time, only 7.2 per cent of the
population – if Stockholm with about 80,000 inhabitants is disregarded –
lived in towns, the majority of which were small. Thus, 29 per cent of the
towns had less than 1 thousand inhabitants, and 63 per cent between 1 and
5 thousand. Three towns had a population of between 5 and 8 thousand,

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[1] Hereafter, both in the text and the tables, the term *square mile* (□ mile) is used
to denote 100 square kilometers (100 km²), and the term *mile* is used to denote 10 kilo-
meters.

Table 3. "Isolate" size in different districts (Dioceses) of Sweden, calculated according to *Dahlberg* on the basis of first-cousin marriages in 1839–1844. Average no. per area unit of marriages contracted 1839–1844 and first-cousin marriages in per cent. Population density and estimated average no. married persons per area unit in 1840. Estimate of marriages contracted in last 6 years as percentage of all existing marriages in 1840. For further explanation, see text.

District (Diocese)	Land area in □ miles (100 km²) (1)	1839–1844			1840			% marriages last 6 years max. estimate (7)
		no. of marriages/ □ mile (2)	% first-cousin marriages (3)	"Isolate" size acc. to Dahlberg's formula (4)	Inhab./ □ mile (5)	no. of married/ □ mile (6)		
1. Härnösand	1,115	10	2.5	250	210	70	29	
	(2,230)	(5)	.	.	(105)	(35)	.	
2. Uppsala	301	44	1.3	490	990	330	27	
3. Västerås a) Dalarna	281	23	1.8	350	490	160	29	
b) Västmanland	80	59	1.0	630	1,390	460	26	
4. Karlstad	221	51	2.1	300	1,220	400	25	
5. Göteborg	144	96	2.1	300	2,360	780	25	
6. Skara	122	93	1.0	640	2,140	710	26	
7. Strängnäs	121	77	0.8	790	1,800	590	26	
8. Stockholm	0.5	[3,721]	0.6	1,060	[84,160]	[27,770]	27	
9. Linköping	171	81	0.9	710	1,830	600	27	
10. Växjö	170	56	1.2	530	1,380	460	25	
11. Kalmar	56	90	0.7	910	1,930	640	28	
12. Lund a) Skåne	109	153	1.7	370	3,540	1,170	26	
b) Blekinge	29	147	1.2	530	3,310	1,090	27	
13. Visby	30	57	2.7	240	1,350	450	26	
The whole country	2,953[1]	45	1.5	420	1,030	340	26	
	(4,068)[2]	(33)	.	.	(770)	(250)	.	

[1] Excluding half of D1 and the capital, Stockholm.
[2] Including the whole of D1 and the capital, Stockholm.

three between 10 and 13 thousand and one, Göteborg (the next largest to Stockholm), had somewhat over 20 thousand inhabitants.

The frequency of married persons in 1840 can be estimated at about 33 per cent. If this rough average for the whole country is applied to the figures in column (5), the figures in column (6) are obtained. Obviously, objections can be raised to this procedure. It would, however, be extremely laborious and costly to elaborate exact figures, and those given can suffice for a rough orientation. We then approximate the figures in column (6) for

the population of 1840 to be the same in 1844 (there was, actually, a slight increase, which is disregarded).

We then calculate twice the figures in column (2), i.e., two persons for each married couple, as a percentage of those in column (6). This gives in column (7) an estimate of those who contracted marriage during the past six years in per cent of all existing marriages. With respect to the approximations, it is interesting to note the small variation in different districts in the number of marriages during the last six years calculated as a percentage of all existing marriages, an average 26 per cent for the whole country. It is perhaps not too bold to conclude from this fact that, during a period of about 25 years, practically all marriages existing at the beginning of the period are replaced by new ones in one district. Thus, from the practical point of view – the population of Sweden in the middle of the 19th century – 25 years could be said to embrace one generation. It can be borne in mind that, at the time in question, the mean age or expectation of life in Sweden largely coincided with the end of the fertile age.

We now compare the figures in column (3) – and (4) – with those in column (2) – and (6).

The figures listed in columns (2) and (6) are averages for the respective districts, and there are naturally large variations within a district around these averages. A more detailed analysis is therefore indicated. In particular, it must be assumed that, in the largest district in the north, the population was at the time distributed very unevenly, with some parts much more densely populated than the average and others between them consisting almost entirely of waste land. It is conceivable that the relatively high frequency of first-cousin marriages[1], persisting until the present day, combined with such a subdivision, a factor acting in the same direction – i.e., a decrease in heterozygosis of the population – could then be so effective that this part of the country has differed to some degree from the other parts, even up to the present time. To ascertain whether this is actually the case, it is, however, necessary to make special studies of the size of any balancing migration (see e.g. *Sjögren* 1948, *Larsson & Sjögren* 1957).

But for the time being, it is reasonable to assume that the aforementioned subdivision, and the sparsity of the population – forcing a candidate for marriage to move over larger areas to *avoid* cousins as a marriage partner – could explain the high frequency of such marriages in the north, above the figure for the whole country.

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[1] Provided that this could more than compensate for the outbreeding effect, due to the non-occurrence of brother-sister marriages.

If first-cousin marriages occurred at random, some such negative correlation, i.e., lower frequencies in more densely populated districts and *vice versa*, could be expected in the rest of the country as well. However, a glance at Table 3 shows that this is not so. In the most densely populated district, Skåne, the western part of D.12 (Lund), the figure is 1.7 per cent, and in the other districts with the highest frequencies, i.e., D.4, D.5 and D.13, we find population densities far above the average. Moreover, the south-west plain part of Skåne, by far the most densely populated area, has a higher frequency of first-cousin marriages than the north-east, less densely populated forested region. In addition, in the central and southern parts of the country, we cannot count on any geographic, topographic barriers sufficiently effective to split the population into small subgroups. Naturally, there was not any random mating in the whole population. To quote *Wahlund* (1928), there may be "isolation", but no "isolates". In making this statement, he had in mind "isolation by distance", when trying to reconcile the then new, more rigid isolate concept with migration viewpoints.

Some relation may, of course, exist between the first-cousin marriage rate and, for instance, the intensity of migration, not in an "isolate" but in an area in general. But such studies are still to be done, and the relation is far from clear-cut. Some flat regions, such as D.12 and D.13, have a high population density and migration rate, and no trace of "geographic, topographic barriers"; their first-cousin marriage rate is the same as, or higher than, that of forest regions, e.g. D.2, D.10 and D.11, where such barriers could possibly be envisaged. The different estimates of "isolate" size according to *Dahlberg*'s formula are difficult to evaluate as measures of the population structure in the respective districts.

It could be inferred from Table 2 that, during the three 5-year periods 1830–1844, the different levels of first-cousin marriages were relatively constant in the respective parts of the country.

During the past 100 years, the population of Sweden has increased by slightly over 100 per cent, and intermigration has become intensified. Consequently, investigations of the frequency of first-cousin marriage in our days in rural population samples from different parts of the country are highly interesting in this connexion. Such studies have been made by *Sjögren* (1948), *Böök* (1948, 1953), *Larsson & Sjögren* (1954), *Böök & Måve* (1955), *Larsson* (1956) and *Fracarro* (1958). The localities investigated were in the north, west and south of Sweden, and the figures recorded were largely of the same order of magnitude as those in Table 2, calculated for 100 years earlier. Those found for the north are perhaps not so surprising, but

the figures computed by *Sjögren* and *Larsson & Sjögren* for district D.5, i.e., 2.4 and 3.1 per cent, are more unexpected, as is that recorded by *Larsson*. In an investigation of a rural parish in the plains of Skåne in the southern part of district D.12, the latter author found the frequency of first-cousin marriages to be 1.7 per cent. Curiously enough, this is the same as the average figure in 1840–1844 for the south-west, most densely populated part of D.12 (see Table 2).

Romanus (1953) has published some figures concerning first-cousin matings in Sweden, but since his series is highly selected, namely, applicants for legal abortion, it does not seem possible to draw any conclusions from it. Of interest is, however, his statement that *Dahlberg* found a first-cousin marriage rate of 0.5 per cent "for schoolchildren" (must obviously mean their parents) in a locality in district D.7 (cf. the corresponding figure, 0.8 per cent, in Table 2).

Cavalli-Sforza (1956/57) has reported an interesting population-genetic investigation from the Diocese of Parma, Compartimente Emilia, in the north of Italy. Altogether 273 parishes were investigated with respect to the frequency of first-cousin marriages, as well as other kinds of consanguineous relationships, population size and height above sea level. The latter factor, i.e., mountain locality, seemed to have a possible relation to the frequency of first-cousin marriages in larger villages, especially those with from 1,100–5,000 inhabitants (see Table 2, p. 396 in *Cavalli-Sforza*'s paper). This group represented 14 per cent of the number of villages investigated. From the tables, this group can be estimated to comprise 40.6 per cent of the whole population sample, with an average 0.57 per cent first-cousin marriages, ranging from 0.5 to 1.4 per cent with height above sea level.

Even if the altitude did not show any marked effect on the first-cousin marriage rate – or was not so clearly associated with it – the size of the village was definitely associated. An interesting observation is that this association was almost entirely bound to villages with less than 300 inhabitants, with an average 2.28 per cent first-cousin marriages. However, even in the next group in size, villages with 300 to 599 inhabitants, the rate decreased sharply to 0.67 per cent, corresponding approximately to the average for the whole population sample. It is also interesting to note that the variation in first-cousin marriage rate with altitude seemed to be completely lacking in the group of parishes with less than 300 inhabitants. This group represented 26.4 per cent of the total number of villages investigated, and can be computed to be 7.6 per cent of the whole population sample.

With all due reservations, *Cavalli-Sforza* calculated the "isolate" size according to *Dahlberg*. The calculations for the group of smallest villages are of particular interest, since they could be expected to be more of an "isolate" nature. With the help of the data in *Cavalli-Sforza*'s Table 2, i.e., $c = 0.0228$, and n (isolate size) $= 238$, we can compute an average 2.22 children per sibship. The calculated size of the "isolate" is in close agreement with the average village size. It would then be reasonable to assume that first-cousin marriages really occur at random in such a village. Under conditions of panmixia, the number of expected brother-sister matings would then be 0.51 per cent. Since these do not occur, 2.1 per cent first-cousin marriages above the 2.28 per cent occurring at random are required for compensating up to panmictic conditions, or an over-all rate of 4.3 per cent. The lack of this compensation implies a higher frequency of heterozygotes within the village than in real panmixia. This negative inbreeding effect – which is too often overlooked – has been elucidated and stressed in a number of papers by *Bernstein* and his school.

However, even small villages are usually in close connexion with their nearest "neighbourhood". Without a study of these connexions, it is difficult to evaluate the first-cousin marriage rates found in these villages. Although such rates may have a special interest, of which we still have little knowledge, it is nevertheless possible that they are of subordinate importance in the study of the genetic population dynamics in human societies.

It seems easier, on the other hand, to evaluate the first-cousin marriage rates in such rarer cases in which the "island" model is really applicable. This applied to a small Protestant subpopulation, emigrating in about 1740 from Pfalz to a purely Catholic region on the Lower Rhine. A brilliant study of this real "isolate" was made by *Bernstein*'s pupil *auf der Nöllenburg;* among other matters, he investigated the hereditary influence on length of life. He used *Wright*'s method of path coefficients in a fruitful way as early as 1932, at a time when the method was seldom encountered in the non-Anglo-Saxon literature. Since the group was, practically speaking, closed ("geschlossene Population"), the random chance of first-cousin marriages could be estimated at 2.7 per cent. The observed rate was 3.7 per cent. This can be computed as about 1 per cent less than the frequency of first-cousin marriages required for compensation of the non-occurrence of brother-sister matings. With respect to panmictic conditions, the frequency of heterozygotes was somewhat raised, even in this small, really isolated subpopulation.

Auf der Nöllenburg's conclusion that a high frequency of mental defectives, when found "in regions with high inbreeding", cannot be ex-

plained by an increase of the homozygotes there due to this inbreeding, then seems reasonable. Such a high rate of first-cousin matings as that required to counterbalance the outbreeding effect in question appears only seldom to be encountered in Western human subpopulations. When such a rate does occur, it seems to be an exception of somewhat special interest.

We must, however, bear in mind that in such small, really "isolated" subpopulations, even with "maximum avoidance of inbreeding within each generation, the heterozygotes continue to decrease. The decrease is a property of the limited size of the breeding group". (*Li* 1955, p. 215).

As *Buzzati-Traverso* pointed out at the Cold Spring Harbor Symposia in 1950, Italy has detailed statistics regarding first-cousin matings in different geographic regions. *Fraccaro* (1957) has given an account of the 1953 statistics, and also made calculations of the "isolate" size according to *Dahlberg*. He mentioned some possible uncertainties in the official statistics, observed by *Serra*.

A tendency of the same nature as that found in Sweden 100 years ago and which, after all, still appears to exist to a certain extent, is found in Italy today i.e., geographic differences. It therefore seems of interest, with reservations for the aforementioned uncertainties, to investigate these conditions over a longer period in different regions of the latter country.

In the following, I have computed and compared the figures for first-cousin marriages in a few districts (compartimenti) of Italy during the periods 1897–1918, 1926–1940 and 1952–1955. The districts compared are two in the north, Piemonte and Liguria, two in central Italy, Toscana and Abruzzi e Molise, and two in the far south, Campania and Basilicata. The figures have also been computed for Sicily and Sardinia, as well as for Italy as a whole. Data on "cousin marriages" – which can be presumed to mean first cousins – are also given in the Italian official statistics for 1868–1883 (see Popolazione 1896–1900; 1897, p. XXI). Despite their uncertainty, these figures are also given, in order to permit a comparison with the statistics for later periods in Table 4. This comparison is, however, left to the reader. In the following discussion, only the later periods will be taken into account.

At the end of the 19th century and the beginning of the 20th, first-cousin marriages in the whole Italian population amounted to about 0.5 per cent of all marriages contracted. During the years preceding World War I, the figures started to decrease, the lowest level, approximately 0.2 per cent, being reached in the years around the end of the War. This was followed by a slow, steady increase, and the figures now seem to be on about the same level as at the beginning of this century. It does not appear

Table 4. First-cousin marriages in Italy (1868–1883), 1897–1939 and 1952–1955, mainly in 5-year periods. Frequencies for two compartimenti in northern, central and southern part of the country, respectively, as well as for Sicily and Sardinia. No. of inhabitants per square km.

Period	Northern Italy		Central Italy		Southern Italy		Insular area		Average of all Italy (9)
	Piemonte (1)	Liguria (2)	Toscana (3)	Abruzzi e Molise (4)	Campania (5)	Basilicata (6)	Sicily (7)	Sardinia (8)	
1868–1869	1.22	1.54	0.37	0.23	0.19	0.31	0.77	0.70	0.70
1870–1874	1.74	1.92	0.36	0.22	0.22	0.35	0.93	0.55	0.73
1875–1879	1.31	1.81	0.39	0.27	0.25	0.39	1.14	0.54	0.66
1880–1883	1.08	1.69	0.29	0.20	0.23	0.28	1.02	0.55	0.58
1897–1899	0.88	1.01	0.20	0.18	0.17	0.42	0.89	0.44	0.45
1900–1904	0.97	1.04	0.17	0.26	0.17	0.33	0.87	0.47	0.49
1905–1909	0.78	0.98	0.25	0.37	0.23	0.40	0.82	0.44	0.47
1910–1914	0.73	0.74	0.16	0.29	0.20	0.24	0.79	0.47	0.40
1915–1918	0.40	0.39	0.11	0.15	0.18	0.11	0.38	0.34	0.22
1919–1925	—	—	—	—	—	—	—	—	
1926–1929	0.29	0.39	0.17	0.46	0.23	0.28	0.94	0.52	0.34
1930–1934	0.35	0.40	0.24	0.49	0.39	0.42	1.43	0.75	0.44
1935–1939	0.37	0.59	0.18	0.51	0.34	0.63	1.14	0.79	0.41
1952	0.24	0.13	0.22	0.51	0.64	0.51	1.75	0.79	0.48
1953	0.20	0.08	0.15	0.58	0.54	0.71	1.65	0.73	0.45
1954	0.20	0.15	0.17	0.67	0.52	0.91	1.65	0.52	0.46
1955	0.14	0.20	0.12	0.42	0.53	0.58	1.34	0.78	0.39
No. of inhabitants per square km									
1871	99	158	89	74	153	48	88	26	90
1901	113	204	106	87	194	49	137	33	113
1931	119	264	126	97	258	51	154	40	133
1951	138	288	137	110	319	63	174	53	157

reasonable to ascribe these changes chiefly to uncertainties in the statistical data. In the first place, marriage between first cousins requires a dispensation in Italy. Secondly, the official demographic statistics are well developed in this country – to a greater degree than in many other European countries – and much interest has been focused on them.

Even if the first-cousin marriage rates for the whole country have not undergone much change, interesting trends can be observed in certain districts.

In the beginning of the present century, the two northern districts –
Piemonte and Liguria – showed fairly high rates for first-cousin marriages;
they were more or less constant, and amounted to about 1 per cent of all
marriages contracted. A relatively slow decrease then took place, the
minimum being reached at about the same time as in the general population.
After a subsequent slight, transient rise, the rate fell and is at the present
time far below the average for the total population.

Of the two districts in central Italy, Toscana seems always to have had
a low frequency of first-cousin marriages. Early in the 20th century, this
also applied to the other district in central Italy, Abruzzi e Molise. After
World War I, an increase occurred in Abruzzi e Molise, and the rate is
now between 0.5 and 0.6 per cent of all marriages.

In the two districts in southern Italy, Campania and Basilicata, an
opposite trend to that in the northern part seems to have been present
during the past 60 years, i.e., low rates in the beginning of the century,
and fairly high ones at the present day.

Sicily in particular, but Sardinia as well, had a fairly high frequency
of first-cousin marriages even at the beginning of this century. A clearly
evident and even marked decrease followed, with the minimum reached
at about the same time as in the general population. This was, however,
succeeded by a pronounced increase. In Sicily especially, a steady, marked
increase can be noted; at the present time the first-cousin marriages have
risen to about 1.7 per cent of all marriages. Using this factor as a basis
for the relevant "isolate" sizes, these would appear to be undergoing a
reduction in present times, which is perhaps an unreasonable process.

As discussed earlier, it appears fairly probable that marriages between
first cousins do not occur at random, and therefore are not useful for
population-genetic calculations. It is nevertheless apparent that significant
differences are present between various districts in Italy of today, as well
as in Sweden more than 100 years ago, and it is probable that this still
applies to the latter country. Furthermore, the respective trend in different
parts of the country seems to lie on a relatively constant level.

This makes it reasonable to presume that in a certain region – at any
rate during a certain period – factors of a relatively constant nature are
present, which produce those first-cousin marriages that occur, or which
act against such marriages in other regions. It might seem plausible to
assume differences in population density as a factor of this nature. This
does not, however, seem to be the case, as was shown earlier with respect
to the Swedish population, nor does it seem to apply in Italy today. This
can be inferred from Table 4, in which are given the figures for the popu-

lation density in different districts of the latter country. These figures are listed, by time periods, at the bottom of the table.

As a further illustration, mention can be made of Firenze and Grosseto in the compartimente of Toscana. In 1871, the areas of these two districts were of about the same order of magnitude, i.e., 58.7 and 44.2 square miles, respectively (one square mile = 100 km²). In 1868–1872, the average population density was 131 persons per km² in Firenze, and 24 in Grosseto. The frequency of cousin (presumably first-cousin) marriages was 0.24 per cent of all marriages contracted in Firenze, and 0.10 per cent in Grosseto. These figures remained fairly constant throughout the 1868–1883 period.

Thus, to sum up, it seems reasonable to conclude that the degree of population density in a particular region appears to have only a fairly slight influence, if any at all, on its first-cousin marriage rate.

It seems fully evident that, in former times, the *non*-occurrence of first-cousin marriages in Western societies was the effect of a "tradition", socio-psychologic in nature. Even in modern times, such a tradition continues to act in preventing matings between relatives of closer degree, e.g. brother-sister. It might therefore be plausible to assume that a "tradition" could also act in the opposite direction, i.e., to promote matings between cousins. In certain groups and societies where a high frequency of first-cousin marriages is found, this seems, in fact, to be unquestionably the case. Examples are the Swedish nobility (see Section V in this paper), the Hohen-zollern Jews (*Reutlinger*) and the population of Japan (see *Neel et al.* and *Schull et al.*). The figures recorded in Western populations are, however, of far lower magnitude, less than 1 per cent or maximally only a few per cent. Despite these low levels of magnitude, often giving fairly diminutive differences from subpopulation to subpopulation, they remain fairly constant, in a way discussed in the aforegoing. It therefore seems feasible to put forward the following hypothesis.

The factors responsible for the said differences are not a "tradition" of the kind discussed, but consist of more "blindly" acting factors, inherent in slight differences between the demographic structure of various sub-populations. One such factor – of several possible ones – was mentioned briefly on page 306. It is, however, beyond the scope of this paper to take up this problem in greater detail. For this purpose, a special, exceedingly extensive investigation is required. It suffices here to point out that the population statistics for Sweden and Italy seem to offer excellent possibilities for such an investigation.

Whatever the relation between the first-cousin marriage frequency and the hypothetical demographic factors may be, it does not, however, seem

to be a very simple one. On the contrary, it is more reasonable to anticipate a relation of a more complex nature. It does not appear to be such a simple matter as that such marriages occur "at random" within more or less closed "pockets" or "isolates" in the population, allowing calculations of their size. Such calculations are difficult to evaluate with respect to human populations, which seem, as a rule, to have a more continuous distribution. Obviously, this "continuous" distribution may be – and often is – of varying intensity or density. In principle, this does not change the difficulties, nor the objections, associated with evaluation of figures calculated according to the oversimplified "isolate" concept. In the following section, an attempt will be made to apply an apparently more fruitful approach from the population-genetic viewpoint for estimation of subpopulations.

IV. PRELIMINARY REPORT OF A STUDY OF ISOLATION
BY DISTANCE, ACCORDING TO WRIGHT, IN FOUR
SWEDISH SUBPOPULATIONS (PARISHES); GEOGRAPHIC
MARRIAGE PATTERN FOR A SMALL TOWN;
MARRIAGES CONTRACTED IN 1800–1824

When dealing in practice with such problems, we have to use statistical data from the smallest administrative units available, i.e., in rural areas, the parishes. When estimating such factors as effective size and migration rate, the so-called island model has generally been used. This was the case in *Dahlberg*'s and *Wahlund*'s pioneer population studies, for instance. Insufficient regard seems, however, to have been paid to what appears to be the chief isolation factor in human populations, namely, that by distance. Even if some reservations were made, too much stress was laid on imaginary isolate barriers in a discontinuous sense. Such discontinuous barriers nevertheless seem to have been fairly infrequent in Western populations, where a more continuous distribution is the rule, with the obvious exception of national borderlines, for example. Moreover, the human being appears always to have been a highly mobile animal, not only in our times, when this mobility has been greatly increased by technical advances.

But mobility is one matter, and mating over a shorter or longer distance is another. This was stressed by *Sjögren* (1948) and *Larsson & Sjögren* (1954) in their investigations of west Swedish rural subpopulations. The crude migration rates may be difficult to evaluate, giving only a rough idea of the genetic structure or dynamics of a population. It is necessary to investigate the matings really occurring within an area, with regard paid to the distance between the birthplaces of the partners and their offspring, and this over several generations. The importance of such a dynamic approach, worked out by *Wright* in a number of papers, was stressed even for human genetics by *Morton* (1955), among others.

Sutter & Tabah (1956/57), pp. 388/89) have stated that it may be easy enough to apply *Wright*'s approach in cattle breeding, with its good

genealogy, and thanks to artificial insemination, by which it is possible to spread genes over long distances. It is not the same thing in the human species, they write.[1]

The authors' conclusions seem to be based on some misunderstanding. Calculation of the stated kind of spreading of the bulls' sperm (in artificial insemination) is presumably of greater interest in a study of the organization of the postal service of a country, but of less interest for studies of the genetic dynamics in so-called natural populations.

Sutter & Tabah expressed the view that insurmountable difficulties are encountered in determining the birthplaces of both parents and children over several generations, with the help of demographic statistics. They suggested instead, if *Wright*'s approach is to be tried, basing the calculations on "les domiciles des époux sur plusieurs générations".

In answer to this objection, it can be pointed out that, in certain Western societies with well-organized population statistics, it is indeed possible to estimate the birthplaces over several generations. Obviously, in those societies lacking such possibilities, *Wright*'s approach cannot be applied.

In such cases, any exact idea of the genetic dynamic structure is impracticable. An individual may, in the course of his life, change his domicile several times. It may then be difficult to decide which of these places of domicile should be included in the calculations, and an arbitrary decision must be made.

It has, however, been shown by *Roberts* (1956, 1956 57), in an interesting and important investigation, that it is well possible, if the necessary, somewhat laborious work is done, to apply *Wright*'s approach even to so-called native populations. This seems to be the first time that the model of isolation by distance has been proved fruitful for such native populations. Hitherto, such studies appear to have been based chiefly on the "island" model. Although this involves less work, it may – owing to its over-simplification – lead to incorrect conclusions. *Roberts*' (1956 57) final words are in contrast to the resigned hesitation of *Sutter & Tabah* with respect to application of the method (isolation by distance) in man, in comparison to animals. *Roberts* wrote: "For the human group is able to provide a wealth

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[1] «Dans l'optique de Wright, qui s'applique à des problèmes d'élevage d'animaux, on préconise de calculer la dimension de l'isolat et son évolution à partir de l'étude de la variance des distances séparant les lieux de naissance des parents et des enfants. Si cette opération est facile pour les bovidés où les généalogies sont régulièrement publiées et où chaque taureau, grâce à l'insémination artificielle, est capable de féconder un grand nombre de vaches et de transmettre des gènes à de longues distances, il n'en est pas de même dans l'espèce humaine.»

of information not available in populations of simpler, more frequently studied organisms."

In the following, a preliminary report will be given of an investigation on mating combinations by distance between birthplaces in certain sub-populations (parishes) in Sweden. It forms part of a study of the frequency and heredity of the major psychoses in the county of Östergötland, the largest part of Diocese 9 (see Fig. 1). The material derives from the central mental hospital in Vadstena during the periods 1900–1910 and 1930–1935. This investigation is being made at the Psychiatric Clinic, Karolinska Sjukhuset, together with Dr. Kj. Fastborg and Dr. D. Kay.

In order to obtain an idea of the genetic-statistical background of the population in the county, certain parishes – both of the plains type and the forest type – are being investigated as follows. The mating combinations for several periods up to about 1860 are recorded from the Provincial Archives (Landsarkivet) in Vadstena. For later periods, the collection of data will be extended to the respective parishes, where the registers for these periods are kept.

For comparison, the latter part of the investigation, dealing with the population movement, also covers subpopulations in other parts of the country, as representative as possible.

Of the material hitherto collected, a report will be given in the following of a sample consisting of two parishes in the county of Östergötland, Diocese 9, and two in the county of Västmanland, the southern part of Diocese 3 (see Fig. 1).

County of Östergötland. Parish R-a lies in a marked lowland region in the western part of the county, and has an agricultural population. Parish A-y is situated in a mixed forest and agricultural region in the southern part of the county. The migration fields for this parish have been thoroughly studied, for almost two centuries back, in a series of important and highly interesting papers by *Hägerstrand* (1947, 1950, 1957).

County of Västmanland. Both parishes lie in the northern, central part of the county. Parish K-g is more westerly, and is a mixed forest and agricultural region, with a marked incidence of mines and quarries. Parish M-a is a mixed forest and agricultural region, with no mines or quarries.

Of these four parishes, R-a is by far the smallest, i.e., 0.3 square miles (1 square mile = 100 km^2), with the highest population density. Although M-a is about 10 times larger, its population density is only slightly more than one-fourth that of R-a. Parishes A-y and K-g are about the same size, half that of M-a. The population density of K-g is about the same as that of M-a, i.e., about two-thirds of that of A-y (see further

Table 8). A full description of the demography of these parishes is beyond the scope of this preliminary report. Here, my intention is only to demonstrate an attempt to express, in concrete, empirical figures, the population structure from a genetic-statistical point of view.

The consecutive series of marriages, year by year, contracted in the respective parishes have been collected, and divided into 25-year periods. The birthplaces of the partners and of their children, if any, have been noted. This time-consuming work is still in progress, tracing the families in their eventual movements over the country. In this preliminary study, the birthplaces of their firstborn children are used, since the other material is not yet complete.

Table 5 shows the distribution of the *marriages* by birth parish of the partners in the four parishes in question during the 1800–1824 period. Marriages with both partners born in the parish investigated are assigned to class 0–0. When one partner was born in this parish and the other in a

Table 5. No. of marriages contracted 1800–1824 in four Swedish rural parishes. Distribution of marriages by birth parishes of partners. 0 denotes birthplace within respective investigated parish. For further explanation, see text.

Type of mating	No. of marriages 1800–1824 in parish of			
	R–a	A–y	K–g	M–a
0–0	34	67	66	212
0–1	36	121	61	69
0–2	18	41	18	21
0–3	12	7	4	10
0–4	7	2	5	5
0–5	2	—	5	2
$0 <^6_9$	4	2	4	3
$0-\geq 10$	2	1	2	5
Σ	115	241	165	327
A–A	69	85	27	36
$\Sigma\Sigma$	184	326	192	363
" ? "	2	13	15	5
$0/0 + A^1$	0.40	0.46	0.57	0.74

[1] Including those partners of " ? ", who are born in O.

directly adjacent parish – the "next" parish – the marriage is denoted as 0–1. When the other partner was born in the "next-next" parish, i.e., had to cross one, the marriage is classified as 0–2, and so on. For instance, class 0–5 denotes those marriages in which one partner was born in the relevant parish investigated, and the birthplace of the other was five parishes away, i.e., four parishes separating the birth parishes of the two partners were crossed.

Class A–A comprises the marriages in which both partners were born outside the investigated parish in which their marriage was contracted. To class " ?" are assigned those marriages in which it was not possible to ascertain the birth parish of at least one of the partners. It was, however, checked by the birth register that it was *not* within the investigated area, the "0 parish".

Table 5 gives a rough idea of the distribution over the parishes of those marriages in which one partner was born in an investigated parish and the other outside it. The last row of the table (0/0+A) shows the proportion of married persons born within the respective parish of all those who contracted marriage there during the period in question.

Parishes A-y and M-a are fairly alike in that agriculture and forestry were the dominating branches of industry in both of them. As stated earlier, parish K-g had a strong incidence of mining and quarries. Despite this, there seems to be somewhat better agreement in Table 5 between K-g and M-a, which are close geographically, than between M-a and A-y.

Parish M-a seems to have the most stable population, since 74 per cent of those married in the parish in 1800–1824 were born in it. Table 6 shows, in the same way as Table 5, the distribution of all marriages contracted in M-a in 25-year periods during 1700–1849. As in Table 5, it is evident that the majority of the married couples were born either in the parish itself or in the adjacent marginal zones, the figures being 94 per cent of all marriages in 1700–1724, and 81 per cent in 1825–1849. During the 150 years in question, there is a slight, but significant spreading outwards with respect to the distance between the birthplaces of the partners. This spreading is, however, very slow, relatively small, and seems to have taken place chiefly after the end of the 18th century.

The size of the different parishes may, however, differ considerably even in the same county. It is therefore important to obtain a more exact measure of the distance between the birthplaces of the marriage partners (parents), and between the birthplaces of the parents and those of the offspring. This calculation has been made, and will be demonstrated in the following. Parish A-y in 1800–1824 can serve as an example; the figures

Table 6. No. of marriages contracted 1700–1849 in 25-year periods in the parish of M–a, county of Västmanland (Diocese of Västerås). Distribution of marriages by birth parishes of partners.

Type of mating	No. of marriages contracted in M–a in					
	1700–1724	1725–1749	1750–1774	1775–1799	1800–1824	1825–1849
0–0	169	171	227	210	212	204
0–1	40	39	56	58	69	77
0–2	11	17	10	7	21	20
0–3	3	6	6	6	10	7
0–4	1	1	—	4	5	5
0–5	1	—	—	1	2	2
$0 < {}^{-6}_{-9}$	1	—	2	7	3	21
0–$\geq$10	—	—	—	1	5	4
Σ	226	234	301	294	327	340
A–A	6	12	12	11	36	43
$\Sigma\Sigma$	232	246	313	305	363	383
" ? "	32	34	19	8	5	3
$0/0 + A^1$	0.78	0.76	0.81	0.81	0:74	0.71

[1] Including those partners of " ? ", who are born in O.

are given in Table 7. The number of distances between parent-offspring birthplaces has been grouped in classes, with a class width of 5 km. We make the hypothetical assumption that the spreading of the parents' birthplaces from the centre – to which the birthplaces of the offspring have been concentrated, schematically – takes place on the whole circularly, with a falling tendency, as shown in Table 7. This assumption is, of course, highly approximative, but the model can serve for our purpose here. Actually, the distribution is somewhat asymmetric.

For this distribution in space, we wish to know the distribution of the number of distances between the parent-offspring birthplaces *in one direction*, i.e., a cross-section. We must then correct n in the table for the size of the area in the respective class zones. The area of class zone i, which is limited outwards by r i and inwards by r $i–1$, is $\pi \cdot i^2 - \pi \cdot (i–1)^2 = \pi \cdot (2i–1)$. Since the factor π is a constant, we divide every n, i.e., the number of parents born in the zone, by the factor $(2i–1)$. For the different values of n' obtained in this way, see Table 7.

Table 7. Marriages with at least one child in parish A–y, county of Östergötland (Diocese of Linköping), contracted 1800–1824. Distribution of no. of distances, birthplace parent/ firstborn offspring in class units = 5 km, birthplace of offspring placed in centre. Calculation of distribution *in one direction*, i.e., cross section of total distribution. For further explanation, see text.

Distance parent-offspring birthplaces, class unit = 5 km	$2i-1$	No. of parents distances (n)	Correction for area size $n' = n/(2i-1)$
0–1	1	241	241.00
1–2	3	111	37.00
2–3	5	64	12.80
3–4	7	49	7.00
4–5	9	31	3.44
5–6	11	9	0.82
6–7	13	5	0.38
7–8	15	3	0.20
8–9	17	4	0.24
9–10	19	3	0.16
10–11	21	5	0.24
11–12	23	3	0.13
12–13	25	1	0.04
13–14	27	2	0.07
14–15	29	—	—
15–16	31	—	—
16–17	33	—	—
17–18	35	—	—
18–19	37	1	0.03
19–20	39	—	—
20–21	41	1	0.02
21–22	43	1	0.02
Σ	—	534	303.61

This distribution is highly leptocurtic, $\beta_2 = 30.7$. This could imply two added distributions, both normal, but one with "short-distance movers" and one consisting of "long-distance movers". It does not, however, seem possible to separate the distribution according to any reasonable principle with this effect.

The standard deviation is 0.70 mile (1 mile = 10 km). Twice this standard deviation is taken as the radius, giving an area of 5.8 square miles, the area of the "neighbourhood" (see *Wright* 1950, p. 332). In 1815, A–y had 1,443 inhabitants, of which 568 were married persons. This gives

a density of 400 married persons per square mile (which estimation proved to be in good conformity to the figure for this area given in the actual statistics), with 2,320 married persons within the "neighbourhood" area. At this time, about 90 per cent of all marriages had offspring. The sibships of this time in Sweden might, of course, have been very large, with a mean number as high as that found by *Lasker* in Mexico in our days. Or, they might have been a mean 5–6, with a range from 1 to 18–20 and a variance of 12, as he found. If all these children reached adult age, married and, in their turn, produced offspring, it would imply that the population increased by about $2\frac{1}{2}$ times per generation, which was not the case in Sweden in 1815.

Only those children who grow up and marry are of interest in our calculations. From the population increase in Sweden at that time, we can compute the average number of *such* children per sibship to be 2.35. The estimation of variance maximally 5, and probably is less. (Regarding population size, breeding size and effective size, see further, *Li* 1955, p. 320.)

Preliminary studies of our subpopulations have shown that about 70 per cent of the marriages had offspring growing up to marriage age. The number of such married persons in the above calculated "neighbourhood" area of A-y can be estimated at 1,568.

This "pseudoexact" figure of 1,568 represents an estimate of the number of "actual" parents within the "neighbourhood" from the genetic-statistical point of view, i.e., those producing offspring reaching marriage age. Due to the variation in the number of such offspring of which each parent becomes an ancestor, the effective size, $\tilde{N}$, of the parental population will be less than the aforementioned size of the "actual" number of parents, N^1, which in itself is less than the real number of parents (not to mention the number of married persons, N, within the area). *Wright* – see *Li* (1955), p. 332, formula (9) – has given the general relation,

$$\tilde{N} = \frac{N^1 \bar{k} \, (N^1 \bar{k} - 1)}{(N^1 - 1) \, \sigma_k{}^2 + N^1 \bar{k} \, (\bar{k} - 1)}$$

In the special case where $\bar{k} = 2$, i.e., where the population remains constant from generation to generation, as in most Western societies of our time, we get – see *Li* (1955), p. 322, formula (10) – $\tilde{N} = \dfrac{4 \, N^1 - 2}{\sigma_{\bar{k}}{}^2 + 2}$ If, for instance, $\bar{k} = 5.6$ *(Lasker* 1950), it seems more appropriate to use

the general formula. The general formula gives a larger effective size than that calculated with formula (10), applying in the special case of $\bar{k} = 2$.

But even a value for $\bar{k} = 2.35$ gives a not negligible difference between estimates of $\widetilde{N}$ calculated according to one or the other formula. The general formula has therefore been used in the following. Preliminary investigation has shown that, in this connexion, $\sigma_{\bar{k}}^2 = 5$ may be regarded as a maximum estimate. (If we include *all* offspring born, irrespective of whether or not they grow up to marriage age, the variance will, of course, be greater. The mortality before the age of adolescence, higher in the larger sibships than in the smaller, will decrease the range and, hence, the variance.)

Thus, with the approach described above, we can estimate the effective population size of the "neighbourhood" – i.e., the area from which the parents in parish A-y can be assumed to be drawn at random – at about 1,000 persons. Also taking into account the fact that, at the time, the effective population size of the whole of Sweden was about 400 times as large, it can be assumed that the random local differentiation in this "neighbourhood" might be negligible, i.e., almost equivalent to panmixia (see e.g. *Wright* 1950, Fig. 7, p. 332).

Calculated according to the "island" model, the effective size of parish A-y would have been about 270 mating individuals, taking into account only sibships consisting of children reaching marriage age, and the variance of such sibships.

Calculated according to *Dahlberg*, on the basis of the frequency of first-cousin marriages for this part of the country (see Table 3, column 4), D.9, Linköping), the "isolate" size would have been about 700 individuals mating at random.

It is fully evident that we must agree with *Morton* (1955) that the method elaborated by *Wright*, as well as his "neighbourhood" concept, are much richer in genetic applications than is the method of estimating the "isolate" on the basis of first-cousin marriages. His method is also greatly superior to the so-called "island" model, which can only take into account migration in an area, without regard to the distance of this migration.

A survey is given in Table 8 of all four parishes in question, in the same way as described for parish A-y. The figures for the two parishes in the county of Västmanland are listed in the upper part of the table, and those for the two in the county of Östergötland in the lower part.

In column (1) is given the number of distances, P-Off., between the parent-offspring birthplaces. The area of the parishes, the number of married persons in the respective parishes in 1815, the radius and area of

Table 8. Isolation by distance, "neighbourhood" area and "effective population size". Calculated according to *S. Wright* (1950) on marriages with at least one child, contracted in four Swedish rural parishes 1800–1824.

Parish	No. of dist. P-off. (1)	Area in □ mile (100 km²) (2)	Av. diam. 1 mile = 10 km (3)	1815				"Neighbourhood"				$\tilde{N}_{isl.}$ (12)	Isolate size acc. to Dahlberg (13)	$\tilde{N}T/\tilde{N}_N$ (14)	$\tilde{N}T/\tilde{N}_{isl.}$ (15)	$A/A+O$ (16)
				N. = no. of married (4)	N/ □ mile (5)	Radius in mile = $2 \times \sigma$ dist. (P-O) (6)	β_2 (7)	Area in □ mile (8)	N_N no. of married (9)	$\tilde{N}_N$ = eff. pop. size (10)	Prop. P born within radius (6) (11)					
M–a	626	2.71	1.9	771	285	1.6	15.7	8.5	2,418	1,136	0.82	362	630	363	1,140	0.26
K–g	320	1.40	1.4	378	270	2.0	18.9	12.1	3,267	1,535	0.86	178	630	269	2,318	0.41
A–y	534	1.42	1.3	568	400	1.4	30.7	5.8	2,320	1,090	0.75	267	710	379	1,546	0.53
R–a	298	0.26	0.6	307	1,181	1.4	62.2	5.8	6,848	3,219	0.73	144	710	128	2,866	0.59

(1) number of distances parent-offspring birthplaces.

(2) area size of parish.

(3) average diameter of parish.

(4) N = number of married persons living in parish in 1815.

(5) do. per square mile in 1815.

(6) "neighbourhood" radius = twice standard deviation of distribution *in one direction* of distances parent-offspring birthplaces.

(7) β_2 = fourth moment / squared second moment (with *Sheppard*'s correction) measuring curtosis of said distribution in one direction.

(8) area size of "neighbourhood" = circle area with radius (6).

(9) NN = calculated number of married individuals living within (8).

(10) ÑN = estimated effective population size within "neighbourhood" area (8).

(11) number of parents (P) born within the "neighbourhood" as a proportion of all parents married within the respective parish.

(12) Ñisl. = effective population size according to the "island" model, i.e., based on population living within respective parish in 1815.

(13) isolate size according to *Dahlberg*'s formula, calculated for Dioceses of Västerås and Linköping: see Table 3.

(14) ÑT/ÑN, where ÑT = 412, 674, the estimated "effective population size" of total population of the country in 1815.

(16) ratio of persons born outside respective parish and married within it to all persons contracting marriage there 1800–1824.

the "neighbourhood", and the effective population size of the "neighbourhoods" can be compared. The figures are also given for the effective population size of the parishes calculated according to the "island" model, and the ratio of the effective size of the total population to the estimated effective size of the "neighbourhood". It may be recalled that the radius in column (6) is twice an estimate of the standard deviation of the distribution of parent-offspring distances *in one direction*. In column (11) is listed the proportion of parents with a birthplace falling within this radius. Column (16) shows the proportion of parents born outside the parish. In column (7) is given the value of $\beta_2 = \dfrac{\mu_4}{(\mu_2)^2}$ with Sheppard's correction, showing that all the distributions are highly leptocurtic.

It was evident from Table 5 that the majority of persons marrying within a parish came either from that parish or from a marginal zone around it. It can be inferred from Table 8. column (6), that, in all four parishes investigated, the diameter of this area ranged from about 25 to 40 kilometers, more or less independently of the size of the parish.

The three more forested parishes M–a, K–g and A–y have "neighbourhoods" with an effective population size of about 1,000 to 1,5000 individuals mating "at random". The ratio of the total population of Sweden (effective size) at that time to that of the "neighbourhoods" is about 130 to 380: see column (14). The random local differentiation (due to isolation by distance) can be assumed to be very slight, or almost equivalent to universal panmixia (see *Wright* 1950, p. 334; *Li* 1955, p. 309). This might, of course, apply especially to the plains in which parish R-a is situated, where a figure of about 3,000 does not seem to be an excessively high estimate of the effective population size of the "neighbourhood'.

Since the time in question – 150 years ago – a slow but steady increase in the migration fields has taken place in the population of Sweden, a phenomenon that has been brilliantly studied by *Hägerstrand*.

With respect to migration, most villages and small towns presumably follow a pattern largely similar to that of the rural parishes, with their closest and most intimate connexions to a marginal zone surrounding them. Examples are, however, found of even very small towns that have a wide range of connexions over the country. Arboga, situated in the middle of the central part of Sweden, can be mentioned as an example.

Arboga had 1,688 inhabitants in 1763, and 1,521 in 1815. Owing to its geographic position, the town was a cultural and political centre ever since the early Middle Ages. Many of the most important meetings of the Riksdag in the early history of Sweden took place there. Since the 17th century,

however, the town has entirely lost its former importance, and has led a very obscure existence up to the present day.

Table 9 shows the distribution of the birthplaces of the marriage partners in Arboga during 1750–1774 and 1800–1824, in a similar way to that for the four rural parishes in Table 5. The difference in distribution is striking. Marriages in which both partners were born in the same parish amounted to about 18–20 per cent of all marriages contracted in R-a and A-y, about 32 per cent in K–g and about 58 per cent in M–a. The corresponding figure for Arboga is 4.7 per cent. In 62 per cent of all marriages in Arboga, both partners were born outside the town. The highest corresponding figure in the rural parishes is 36 per cent in R-a, and the lowest 10 per cent in M–a. In 1800–1824, only 21 per cent of all the persons who contracted marriage in Arboga were born there, and in 1750–1774 the figure was 24 per cent.

It might be tempting to assume that people coming from various places merely married in Arboga, and then settled down in their places of origin.

Table 9. No. of marriages contracted 1750–1774 and 1800–1824 in the urban parish of A-a, county of Västmanland (Diocese of Västerås). Distribution of marriages according to birth parishes of partners.

Type of mating	No. of marriages contracted in A–a in	
	1750–1774	1800–1824
0–0	25	15
0–1	14	15
0–2	20	13
0–3	10	7
0–4	21	12
0–5	16	10
$0 <^6_9$	17	14
0–$\geq$10	26	22
Σ	149	108
A–A	179	174
$\Sigma\Sigma$	328	282
" ? "	66	35
0/0+A[1]	0.24	0.21

[1] Including those partners of " ? ", who are born in O.

This was not, however, the case. In about 80 per cent of the marriages with children in 1800–1824, the first-born child was born in Arboga, and in 1750–1774 about 75 per cent. Some of them later moved away; the laborious work of tracing them over the country is now being done.

In 1750–1774 there were 149 marriages in Arboga with at least one partner born in the town, and in 1800–1824 there were 108. The percentage distribution of these marriages by distance in miles (one mile = 10 km) from Arboga to the birthplace of the other partner is given below.

	0–5	5–10	10–20	20–50	50–
1750–1774	62	19	13	5	1
1800–1824	56	21	13	8	2

In 1750–1774 there were 179 marriages in Arboga with neither of the partners born in the town; the corresponding figure in 1800–1824 was 174. The percentage distribution of these marriages by distance in miles (1 mile = 10 km) between the birthplaces of the partners is shown below.

	0–5	5–10	10–20	20–50	50–
1750–1774	47	23	22	4	3
1800–1824	55	25	16	2	2

The percentage distribution of the distance in miles between the birthplace of each marriage partner and the place of marriage (Arboga) is given below for the 1750–1774 period (totally 656 persons) and for the 1800–1824 period (totally 564 persons).

	0–2.5	2.5–5	5–10	10–
1750–1774	43	29	13	15
1800–1824	44	16	27	13

It seems clear that, for Arboga, we have a "neighbourhood" of essentially the same structure as that for the rural parishes, except that it is incomparably larger in size. The distribution in the circle with a 10–mile radius is also asymmetrical. Exact calculations have not yet been made. The analysis of the Arboga material is not completed; moreover, it will certainly be of greater interest to present it together with investigations of some rural parishes situated in the "neighbourhood" of this town. Even

small towns of such a type as Arboga, as well as large villages, may serve as real "pacemakers" or "accelerators" of the gene flow with regard to space, in the background regions in which they are situated. To take into account only the situation in purely rural areas would give a not altogether realistic picture of the gene flow in a population.

Obviously, in comparisons and conclusions such as the aforegoing, it is necessary to make all due reservations for the many uncertainties always inherent in official data on population statistics. But although the figures perhaps give a rough idea of the phenomenon studied, they may be of certain value. Moreover, it seems to me that the approach developed by *Wright* – which I have attempted to follow here, even if in a possibly incomplete way – is nevertheless vastly superior to other methods for an investigation of continuous human populations.

The samples studied here are small, and are taken from two parts of the country[1]. Caution must therefore be observed in generalizing conclusions drawn from them to apply to the country as a whole. It seems probable that, in Sweden at the time in question, there were, in fact, parts where isolation by distance may have played a not negligible role in local random differentiation from the genetic-statistical aspect. This could be expected to be true of the northern part of the country in particular. The most adequate way of obtaining an idea of the possible degree of such a differentiation seems to be along the lines applied in the present study. Material from subpopulations in the north is now being collected for this purpose.

To sum up. In the earlier section IV the difficulties were discussed that are encountered when trying to evaluate the frequencies of first-cousin marriages, in order to obtain an idea of the dynamic structure of a subpopulation from the genetic-statistical point of view. The crude migration rates are also difficult to evaluate in this respect.

A way out of the dilemma for human population genetics is the approach of *Wright*, i.e., the isolation by distance model, which takes into account the distances between parent-offspring birthplaces. Its fruitfulness even in investigations of so-called native populations has been demonstrated by *Roberts* (1956, 1956/57).

As a preliminary report of a larger research programme, an investigation

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[1] In the course of the investigation, further material has been collected, consisting of one parish in Diocese 9, one in Diocese 7 and four in Diocese 3. The distributions for these parishes show a somewhat monotonous similarity to the distributions in Tables 5 and 6.

is presented of a sample comprising four Swedish subpopulations (parishes). The parishes all differ somewhat in character, and are taken two by two from different parts of the country. The marriage-migration fields are given, and clearly show that the chief isolating factor is that by distance. The majority of partners marrying in a particular parish are found either to have been born within it, or in a marginal zone around it. In one parish, the marriage-migration field can be shown to have undergone relatively little change over the generations during the period investigated, 1700–1849. A fairly slow but distinct increase can, however, be noted.

The "neighbourhood" area and its effective population size in 1815 have been estimated for the four subpopulations comprised by the parishes. In view of these estimates and the effective population size of the contemporary total population of Sweden, it is reasonable to assume that, at the time in question, there was no local differentiation from a genetic-statistical aspect in the regions investigated.

In a small town in the central part of Sweden with somewhat more than 1,500 inhabitants, the birthplaces of the marriage partners have been studied during the periods 1750–1774 and 1800–1824. The basic material makes clear the existence of a "neighbourhood" of essentially the same structure as that for the rural parishes described above, except that it is far larger in size. Villages and small towns of this type may act as "pacemakers" for the gene flow in space, i.e., in the larger rural background region in which they are situated.

The object of the investigation is, in the first place, to obtain an idea of the population-genetic background in the county of Östergötland and, thereby, to compare it with that in other parts of the country. A clinical-genetic investigation of the so-called major psychoses is now being made in the county in question. A further object is to try to obtain a conception of the dynamics of the "gene flow" (spreading of a gene) in the country – problems inherent in an earlier study of a rare, monohybrid recessive condition (*Alström & Olson* 1957).

V. THE SWEDISH NOBILITY AS A SOCIAL ISOLATE.
FIRST-COUSIN MARRIAGES 1750–1844;
MIGRATION STRUCTURE IN 1680–1869

The isolation barrier between certain extreme social groups, e.g. the nobility, and the remaining population seems – at any rate in former times – to have been of a more discontinuous nature than the barriers dealt with in previous sections. It therefore appears more adequate from the genetic-statistical point of view to apply the "island" model.

The incidence of consanguineous marriage in the Swedish nobility has been treated in a paper by *Fraccaro* (1958). Using material extracted from *Elgenstierna* (1925/36), *Fraccaro* analyzed the periods 1821–1830, 1851–1860, 1871–1880, 1901–1910 and 1921–1930. The figures for first-cousin marriages were, in the following order, 6.1, 5.0, 3.4, 0.3 and 0.8 per cent. In about 6–8 per cent of the cases both partners were born in the same parish (kommun), and this low frequency was found in all the periods investigated. The proportion of partners born in different counties showed a slight increase from about 75 per cent in 1821–1830 to about 80 per cent in 1921–1930. (The county is the largest civil administration unit, Sweden being divided into 24 counties and the capital, Stockholm.)

Elgenstierna's genealogy covers that part of the nobility introduced at the House of the Nobility (Riddarhuset), i.e., whose names are inscribed on its rolls. The genealogy up to 1875 of the "unintroduced" members of the nobility (i.e., those not inscribed on the rolls of the House of the Nobility) is given in the publication of *Schlegel & Klingspor* (1875).

In his comprehensive study of the Estates of the Swedish Realm, *Carlsson* (1949) presented the extensive material regarding marriages contracted by the nobility in 1680–1869, based on the two aforementioned genealogical works. On the basis of *Carlsson*'s material, as well as my analysis of the records of first-cousin marriages kept in the National Archives (Riksarkivet), I have been able to calculate the frequency of first-cousin marriages in the Swedish nobility in 10-year groups from 1750–1844. The number of marriages in 1680–1869, distributed according to the

different types of mating, has been calculated; these figures are listed in Table 10. The frequency of first-cousin marriages in the different types of mating is recorded in Table 11.

That the "unintroduced" members comprise a not so inconsiderable proportion of the whole nobility is evident from the fact that, in 1820–1829, 42 first-cousin marriages were contracted in the whole nobility. *Fraccaro*'s material, based on that of *Elgenstierna* (the "introduced" nobility only), contains 24 such marriages. *Fraccaro* noted a total 393 marriages in the nobility in 1821–1830, whereas the figure given by *Carlsson* is 672, and this is *exclusive* of marriages between a noble woman and a commoner, amounting to 297. Remarkably enough, the frequency of first-cousin

Table 10. No. of marriages with at least one noble partner, contracted 1680–1869, in 10-year periods. Percentage distribution by different types of mating. Computed, with kind permission, from Tables 37–41, pp. 181–185, *Sten Carlsson* (1949).

Period	Total	Marriages			$F_A/M_A \times 100$
		Distribution in % by mating			
		$M_A \times F_A$	$M_A \times F_O$	$M_O \times F_A$	
	(1)	(2)	(3)	(4)	(5)
1680–1689	527	65	8	27	127
1690–1699	570	58	11	31	135
1700–1709	606	44	11	45	164
1710–1719	935	42	13	45	164
1720–1729	985	49	18	33	127
1730–1739	767	46	22	32	117
1740–1749	912	43	24	33	109
1750–1759	1,017	43	22	35	119
1760–1769	1,046	44	25	31	108
1770–1779	1,009	40	28	32	103
1780–1789	934	41	30	29	96
1790–1799	982	38	31	31	99
1800–1809	920	35	32	33	102
1810–1819	1,041	34	36	30	90
1820–1829	969	30	40	30	86
1830–1839	958	27	43	30	80
1840–1849	1,009	24	41	35	90
1850–1859	1,150	23	42	35	90
1860–1869	1,101	22	45	33	78

M_A = noble man, F_A = noble woman, M_O = not-noble man, F_O = not-noble woman. (5) No. of noble women marrying per 100 noble men marrying (regardless of type of mating): see Table 4, p. 185, S. Carlsson.

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marriages is, however, the same; cf. *Fraccaro*'s 6.1 per cent, and 6.3 per cent in Table 11 for the 1820–1829 period. (Actually, 47 first-cousin marriages were contracted in the nobility in 1821–1830; the lower figure of 42 is due to the displacement of one year. However, *Elgenstierna* as well seems to give a larger number – i.e., 39 – than the extract used by *Fraccaro*.)

It can be inferred from the demographic and genealogical investigation made by *Fahlbeck* (1898) that no difference existed between the social structure of the "introduced" and "unintroduced" part of the nobility. In certain respects, the House of the Nobility could be regarded as a kind of Trade Union, an organization which protected the interests and privileges of its members.

We return to Table 11, in which column (6) shows the frequency of first-cousin marriages for noble men. These matings represent the nobility as a social group. Noble women marrying commoners are to be regarded as emigrants into the population of commoners. Women commoners marrying noble men are, on the other hand, to be regarded as immigrants, and are included in the nobility as a social group.

Table 11. Frequency of first-cousin marriages in per cent of all marriages with at least one noble partner, contracted 1750–1844, in 10-year periods. Distribution by different types of mating.

Period	No. of first-cousin marriages in nobility (1)	Different types of mating							First-cousin marriages in gen. pop. in % (9)
		$H \times H$ (2)	$L \times L$ (3)	$H \times L$ (4)	$M_A \times F_A$ (5)	$M_A \times F_A$ or F_O (6)	$M_A \times F_O$ (7)	$M_O \times F_A$ (8)	
1750–1759	26	13.7	4.8	1.7	5.0	3.5	0.4	0.9	0.3
1760–1769	33				5.3	3.9	1.5	1.5	0.4
1770–1779	34	3.2	10.3	3.7	7.5	4.7	0.7	0.6	0.5
1780–1789	22				4.7	3.0	0.7	0.7	0.6
1790–1799	39				8.5	5.3	1.3	1.0	0.8
1800–1809	36	13.0	11.6	2.1	9.0	5.9	2.4	0.0	1.0
1810–1819	27				6.4	3.3	0.3	1.0	1.1
1820–1829	42	12.7	11.2	4.9	9.8	6.3	3.4	0.3	1.1
1830–1839	45				11.2	6.1	2.2	0.7	1.4
1840–1844	2×17[1]	19.7	15.7	0.0	11.7	5.2	1.5	0.0	1.5

H = high-noble man or woman, L = low-noble man or woman.

Regarding M_A etc. see Table 10.

[1] Frequencies for 1840–1844 somewhat uncertain and approximate, calculated for twice half a ten-year period, no. of all marriages contracted being for the whole period 1840–1849.

First-cousin marriage in the nobility as a social group, column (6), is seen to have a high incidence ever since 1750, when systematic recording became possible. From a frequency of 3.5 per cent, there is a slow increasing trend, and the frequency even exceeded 6 per cent in the decades 1820–1840. The difference between 1810–1819 (3.3 per cent) and 1820–1829 (6.3 per cent), for instance, is 2.6 times it's standard error. This shifting, irregular course of the frequency figures might indicate that, with respect to the factors underlying consanguineous matings, the nobility is heterogeneous, in contrast to the remaining population. The contrast is even more striking in view of the notably even course, with small, apparently random deviations, exhibited by each district separately in the general population. It can be inferred from Appendix 2 how the different geographic districts seem, year by year, to be adjusted to a fairly fixed level of first-cousin matings. On the other hand, systematic differences can be noted between the various districts.

Fraccaro's figures are given above for comparison. It is evident from them that the frequency of first-cousin marriages in the nobility did not fall until about the end of the 19th century. The incidence of first-cousin marriages in the general population is shown in column (9) of Table 11. It can be seen that whereas this frequency rose slowly, as discussed in the previous section, that in the nobility was fairly irregular and many times larger. It is not until the present century (see *Fraccaro's* figures on page 334) that low figures are found in the nobility, lower than in the samples from the general population. The economic factor operating in the general population, manifested in the abrupt rise after 1829, when a dispensation ceased to be a costly matter, cannot reasonably have played any essential role for the nobility. Taken as a group, the nobility was a selection better situated economically than the average.

The matings in the nobility, as shown in Table 10, can be split up into fractions. The following denotations will be used: M_A = noble man, F_A = noble woman, M_O = common (not-noble) man, and F_O = common (not-noble) woman. The frequency of first-cousin marriages in group $M_A \times F_A$ is recorded in column (5), Table 11. High figures are found in this group, amounting to 10 per cent or above in the first half of the 19th century. As early as the middle of the 18th century, the frequency of first-cousin marriages between noble partners, see column (5), is 5.0 per cent, as compared to 0.3 per cent in the general population.

The pure H $\times$ H (high-noble $\times$ high-noble) and L $\times$ L (low-noble $\times$ low-noble) matings show still higher frequencies. During the whole period recorded, 1750–1844, especially those of the H $\times$ H group at times approach

the order of magnitude usually found among parents of patients with rare, monohybrid recessive diseases; see columns (2) and (3), Table 11.

A lower frequency is found for intermarriage between high and low nobility, see column (4). This is, to some extent, an expression of the fact that marriages are less apt to occur between than within these two substrata of the nobility.

The frequency of first-cousin marriages in group $M_A \times F_O$ is much lower and, as could be expected, below the average for the nobility (male) as a whole. It is nevertheless consistently somewhat higher than in the general population; this is particularly marked in the 19th century. The lowest incidence during the corresponding period, even lower than in the general population, is found in group $F_A \times M_O$, i.e., the women emigrating from the nobility as a social group.

It seems clear that, in the Swedish nobility of that time, exactly as in Japan today, first-cousin marriages were highly favoured, and can scarcely be assumed to have occurred at random. Application of *Dahlberg's* formula does not seem to be useful here. On the other hand, the aforegoing figures imply that a not altogether inappreciable degree of inbreeding was present. For instance, for the 1830–1839 period, we can estimate for group $M_A \times F_A$ a mean coefficient of inbreeding, F of ~ 0.007 (203 marriages, of which 31 between first cousins) in relation to that in the general population, from which about half of the Swedish nobility is descended. The corresponding figure for the nobility as a whole ($M_A \times F_A + M_A \times F_O$) is at least $F \sim 0.004$ (675 marriages, of which 41 between first cousins). It is not improbable that, if other relationships could have been taken into account, the value would have been doubled for the high nobility, with its older traditions. This would, however, scarcely have applied to the low nobility, of which the heterogenity will be discussed in the following.

The importance of this inbreeding habit would, of course, be still greater if, at the same time, the group were strongly isolated from the remaining population. Moreover, we know that the nobility has a social barrier within itself, that between the high nobility and the so-called low nobility, the former being the older, more exclusive part.

Let us now consider the migration situation between these two parts of the nobility, and between them and the remaining population. It must be borne in mind that, in this connexion, the "remaining population" probably did not comprise the whole rest of the population, but only a small part of it, which, in itself, is more or less "isolated" from the "whole population".

Table 12. No. of marriages contracted by high- and low-noble men 1680–1869, in 10-year periods. Percentage distribution by type of female partner. No. of high- and low-noble women marrying, and percentage of marriages with not-noble men. Computed, with kind permission, from Tables 37–41, pp. 181–185, *Sten Carlsson* (1949).

Period	No. of marrying M_H (1)	Percentage distribution by			No. of marrying M_L (5)	Percentage distribution by			No. of marrying F_H (9)	Per cent with M_O (10)	No. of marrying F_L (11)	Per cent with M_O (12)
		F_H (2)	F_L (3)	F_O (4)		F_H (6)	F_L (7)	F_O (8)				
1680–1689	65	68	32	—	318	11	76	13	78	—	432	33
1690–1699	48	50	50	—	346	14	67	19	84	4	449	39
1700–1709	43	60	33	7	291	14	64	22	76	4	472	57
1710–1719	75	63	37	—	437	16	55	28	135	9	703	59
1720–1729	92	55	44	1	568	12	58	30	139	10	698	45
1730–1739	85	64	30	6	434	10	53	37	98	7	511	47
1740–1749	102	52	39	9	511	12	47	41	131	17	539	51
1750–1759	118	43	46	11	548	11	50	39	125	10	665	51
1760–1769	110	50	39	11	608	12	47	41	132	9	644	49
1770–1779	119	52	30	18	566	13	41	46	143	15	560	54
1780–1789	138	43	44	13	523	9	41	50	118	14	516	50
1790–1799	146	41	38	21	535	11	38	51	145	19	528	52
1800–1809	119	46	40	14	494	10	35	55	129	23	494	56
1810–1819	166	36	40	24	566	10	31	59	137	21	523	54
1820–1829	153	41	24	35	519	9	27	64	143	24	435	60
1830–1839	160	37	27	36	515	10	21	69	135	22	403	63
1840–1849	158	39	26	35	494	7	21	72	147	33	437	71
1850–1859	197	38	25	37	550	10	17	73	199	35	474	70
1860–1869	180	26	25	49	559	9	17	74	139	37	438	71

M_H = high-noble man M_L = low-noble man
F_H = high-noble woman F_L = low-noble woman

The figures in Table 12 have been computed from Tables 37–41 in *Carlsson*'s aforementioned monograph (pp. 181–185). We use the following denotations: M_H = high-noble man, M_L = low-noble man, M_O = common (not-noble) man, F_H = high-noble woman, F_L = low-noble woman, and F_O = common (not-noble) woman. The total number of high-noble men mating is given in column (1), and the percentage distribution over different mating partners in the columns next in order. In the second section of the table, columns (5) to (8), the matings of low-noble men are treated in the same way. These two sections cover matings in the nobility as a social group.

Columns (9) to (12) in Table 12 show the total number of F_H and F_L matings, and the percentages of these women mating with M_O (not-noble men), and thus definitely leave the nobility as emigrants.

Let us in the following discuss the marriages of noble men, who represent the nobility as a social group or "isolate". We start with the low nobility. During the 17th century and beginning of the 18th, the influx of F_O (not-noble women) was relatively modest, 13 to 22 per cent, and was still under 30 per cent in the 1710's. The influx of F_H (high-noble women) was, however, still smaller; it started by being between 10 and 15 per cent and then – up to 1869, when the statistical series ended – remained as low as around 10 per cent. The marriages of low-noble men within their own group thus predominated during the 17th century and early 18th; it then fell slowly, but still comprised half of all marriages in the 1750's. Thereafter, $M_L \times F_O$ matings increased, so that in the middle of the 19th century the conditions were exactly the opposite of those in the 1680's, i.e., 75 per cent of low-noble men married not-noble women. The figure for marriages with high-noble women, however, still remained at about 10 per cent. As far as low-noble men are concerned, the social barrier to marriage with the high nobility seems always to have been stronger than the barrier to marriage with commoners.

To throw further light on the situation, it is desirable to have some information about the origins of the Swedish nobility. *Fahlbeck's* investigation provides some important data, on which Table 13 is based. It shows, in column (2), in periods adapted to the reigns of the various Swedish sovereigns, columns (3) and (4), the percentage of newly ennobled persons (families) in a cumulative distribution since 1611. Before this year, about 6 per cent (obviously a highly approximative calculation) of all the known nobility had been ennobled. Up to and including 1644, the corresponding figure is still only 11 per cent. Thereafter, rapid progress was made, so that the nobility increased to the double in ten years. Half the entire Swedish nobility as a group was recruited in about 100 years – from 1654 to 1751 – and the median falls around the year 1700. Naturally, many families died out in the course of time, or left the nobility for various reasons. The cumulative distribution, according to the time at which the family was ennobled, of those surviving in 1898 is given in column (4).

Since it was on principle men who were ennobled, a strong, steady influx of male commoners into the low part of the nobility as a social group took place in 1650–1750. It could be inferred from column (8) of Table 12 that, at the time, the influx through marriages with F_O (female commoners) was relatively small. It must, however, be borne in mind that it

Table 13. Cumulative percentage distribution of Swedish nobility by time of ennoblement: main increase during 100 years after 1644. Corresponding distribution of nobility with members (families) alive in 1898. Computations from figures given by *P. Fahlbeck* (1898), p. 459.

Sovereign (1)	Period (2)	All known nobility in % (3)	Nobility with members alive 1898 in % (4)
Earlier	–1611	6	6
G. II A.	1611–1632	8	7
Regency of Chr.	1632–1644	11	10
Chr.	1644–1654	25	18
C. X G.	1654–1660	26	18
Regency of C. XI	1660–1672	31	22
C. XI	1672–1697	52	35
C. XII	1697–1718	62	42
U.E. + F. I	1718–1751	76	56
A.F.	1751–1771	83	69
G. III	1771–1792	89	79
G. IV A.	1796–1809	92	84
C. XIII	1809–1818	96	90
C. XIV	1818–1844	99	97
O. I	1844–1859	99	98
C. XV	1859–1872	100	99
O. II	1872–1898	100	100

was not only the man who was granted a patent of nobility, but his family as well, i.e., wife and children. When the aforementioned influx of commoners through new ennoblements decreased greatly in the later decades of the 18th century, another process was, however, taking place, namely, a greatly increased influx of not-noble women to the nobility as a social group, through $M_L \times F_O$ matings.

It can also be of interest to study in more detail the national origins of the Swedish nobility, with its essential increase during the time when Sweden was a military European power. *Fahlbeck* (1898, p. 473) stated the origin to be Swedish in 67.9 per cent, Finnish-Swedish in 7.9, altogether 75.8 per cent from the Swedish realm of the time. The origin was German in 11.4 per cent, Baltic in 7.6, English-Scottish in 1.9 and the rest, i.e., 3.3 per cent, distributed over Danish, Dutch, French, Austrian, Norwegian, Russian, Swiss and Italian origin. If it is also taken into account that a not inconsiderable number were, before their ennoblement, immigrants

who had become naturalized Swedish subjects, over half of the nobility is of foreign descent. Only 48.3 per cent is of genuinely Swedish origin. It has been said that, when the foreign influx was at its height, two or three languages were spoken concurrently at the meetings in the House of the Nobility.

In view of all these circumstances, it can scarcely be postulated that the majority of the Swedish nobility, i.e., the low nobility, constituted an isolate from the population-genetic point of view. On the contrary, it must have been a particularly heterogeneous group, far more heterogeneous than the rest of the population. At this time, there must have been a positive selection – e.g. with respect to gift and talent – of native and foreign elements from widely divergent parts of Europe in the newly recruited part of the nobility, particularly the low nobility as a social group. A not negligible heterosis effect could have been able to assert itself. It can, however, be presumed that a relatively rapid, effective equalization came into effect through the subsequent influx of female commoners.

Moreover, such properties as intelligence are, in fact, essentially determined multifactorially. Further, ennoblement as a selective factor in this respect had practically ceased after the beginning of the 19th century. Consequently, it is likely for several reasons that an equalization vis-à-vis the not-noble part of the population took place relatively quickly after this time.

The aforegoing discussion is chiefly concerned with the low part of the nobility. The high nobility was a more closed social group, as can be inferred from Table 12. It is interesting to note that up to 1730 practically no $M_H \times F_O$ marriages occurred, or only very few, and even in the early 19th century such matings were fairly limited in number. Subsequently, in this group as well, the influx of female commoners strongly increased, representing half of all marriages in the nobility during the 1860's. The proportional influx into the high nobility group of F_L (low-noble women) through marriage has changed relatively little through the centuries. Obviously, an appreciable mass of genetic elements of pure non-noble origin passed into the high nobility via the F_L. This also took place via a not inconsiderable influx of low-noble men, raised to a higher degree of nobility as a reward for their achievements. Here as well, it is necessary to assume a positive selection of men in the respect discussed above. Apart from a slower rate, the same equalization vis-à-vis the not-noble part of the population should reasonably have taken place.

Despite the apparently high degree of inbreeding, it can be assumed that, in the high nobility as well, there was a fairly intense equalization in re-

lation to the not-noble part of the population. In a statistical cross-section, this group might seem rather small, some hundred M_H marrying per generation. In a totally closed group, this would imply a rate of decay of variability that is not negligible, if allowed to act undisturbed over several generations. The effect of genetic drift may, however, have been counter-balanced by the relatively high immigration which did, in fact, occur. This can be demonstrated by some simple calculations.

Wahlund (1928), when treating the isolation problem, had the "island" model in mind. He gave the formula (p. 94, formula 3a):

$$(r_{sn} - r_x) = (1 - a_{s1}) \cdot \ldots \ldots \cdot (1 - a_{sn}) \cdot (r_s - r_x)$$

in which, at the beginning of the "breaking down of the isolate", r_s is the frequency of a certain gene in an isolated group, and r_x is its frequency in the population outside the group. In each generation, a_{si} immigrants come from the population into the group, with corresponding emigration in exchange. The gene frequency in the "isolate" after n generations is denoted by r_{sn}. It is assumed that the frequency, r_x, in the population outside the group is constant during the n generations, and that the size of the population within the isolate is constant.

These conditions were, with all certainty, not fulfilled in the high nobility during 1680–1869. But let us, to facilitate the calculations, assume that this was the case. We divide the material in Table 12 into 30-year periods, artificially corresponding to the successive generations, and let the decade 1860–1869 represent one generation. We then get 7 generations during the period in question. Since the low nobility clearly showed its intimate relations with the population of commoners, F_L and F_O are combined, as more or less equivalent, into the immigrant group, a_{si}.

The difference between the gene frequency in the high nobility and the immigrants, in view of the situation in 1680 and 1860, can then be computed easily with *Wahlund*'s formula 3a. The difference can be derived from the equation $(r_{s7} - r_x) = 0.1 \cdot (r_s - r_x)$, i.e., the difference in 1870 is one-tenth of the original one.

If, at the hypothetical beginning of the breaking down of the "isolate", some gene had been fixed within the nobility, e.g. $r_s = 1$, and its frequency outside the group, r_x, was practically equal to zero, the frequency of the gene had fallen to 0.1 in these 7 generations. If sex-linked, the frequency of the gene had decreased to 0.04. The remainder had disappeared beyond the "isolate" borders. It is considered that a coincident high degree of inbreeding does not affect the gene frequency within the isolate. It has

an effect only on distribution of the gene over different types of zygotes within the "isolate".

The fictitious example gives an initial maximal gene difference between the population in and outside the isolate. It is, of course, reasonable to assume that the initial gene differences are much smaller in actual fact. The aforegoing calculations have been done merely as a schematic illustration. Admittedly, they may seem naive, since matters are far more complicated in Nature. However, all these complications seem to act in one direction, decreasing the differences calculated in the aforegoing way.

One important objection is that the high nobility as a social group was not constant in size. It showed steady growth, owing to an influx of male immigrants from the low nobility. Moreover, this process continued even when the low nobility had ceased to increase, i.e., with the great decrease in the number of ennoblements. This is apparent from Table 12, showing the number of men of the high nobility of those who contracted marriage in the generations listed, in comparison to the corresponding number in the low nobility. This growth of the high nobility should, however, still further raise the "dilution".

To sum up. The Swedish nobility had a high degree of first-cousin marriage already in 1750, when the corresponding frequency was very low in the general population. It seems, however, clear from available data that this high first-cousin marriage rate in the nobility cannot have dated further back than at most 50 years. Before this time, first-cousin matings were rare exceptions in all classes of society.

The first-cousin marriage rate seems to have remained on about the same high level during the whole period investigated (1750–1844), and did not show a decrease until the second half of the 19th century. It was highest in the high nobility and the low nobility taken as separate groups. In fact, at least in the high nobility, it approached the degree of first-cousin mating found among parents of patients with rare, monohybrid recessive diseases. It by far compensated for the outbreeding effect, caused by the non-occurrence of brother-sister matings in human populations, with regard to panmictic conditions.

Accelerated through this degree of inbreeding, there is reason to assume a not negligible rate of decay – at any rate in the high nobility – provided that this group was closed, or had a very low migration rate.

However, a study of the growth of the Swedish nobility and its substrata, and of their migration pattern, computed from the basic material of *Carlsson* and *Fahlbeck*, has shown the contrary to apply. During the time

for the main increase of the nobility as a social group, most immigrants were not-noble males; thereafter, up to our time, the immigration was practically confined to a large number of not-noble women through marriage. Especially during the moulding time of the Swedish nobility, which took place essentially during about 100 years, i.e., from the middle of the 17th century to the middle of the 18th, a considerable heterosis effect cannot be ruled out, combined with a positive selection. It can also be borne in mind that somewhat less than half of the nobility is of genuinely Swedish descent, the remainder deriving from various parts of Europe.

GENERAL SUMMARY

Relation Between Frequency of First-Cousin Marriages and Isolating Factors in Human Populations

1. *Dahlberg*'s well-known approach for estimating the size of "genetic isolates" on the basis of the frequency of marriages between relatives in a population is discussed. The two chief sources of error inherent in it are mentioned. One is the difficulty of obtaining complete data regarding marriages between more remote relatives. Moreover, the practical difficulties involved in checking such data are almost insurmountable. The second source of error applies to matings between close relatives, namely, that they do not occur at random. This is especially true of matings of the aunt-nephew and uncle-niece type, which can reasonably be assumed to occur far less than at random.

Marriages between first cousins are more important and useful in this connexion. Such data are easier to obtain, and genealogical checking is practicable. Doubts can, however, arise regarding their random occurrence, and the calculated frequencies are difficult to evaluate, except in closed population samples.

2. In some countries, a decrease in the frequency of first-cousin marriages has taken place in recent times. Without more extensive investigation of this phenomenon, it cannot be generalized to apply to "most European countries", at any rate up to World War II.

3. The type of consanguineous mating dealt with must be specified. Data merely on "the frequency of consanguineous marriages" are completely impossible to evaluate.

4. Brief mention is made of the historical development in Western societies of the taboo against marriage between relatives, that between first cousins being of particular interest here. The role of the Catholic Church and of canon law is touched on. Cessation of the prohibition against first-cousin marriages with advances of the Reformation in Europe. Sweden an exception; the prohibition is maintained, owing to the attitude of the Protestant Church in this country. Introduction of dispensation by King in Council in 1680. Removal of the prohibition in 1844.

5. Organization of the Swedish population statistics in 1749. First-cousin marriage rates in Sweden 1750–1844, calculated on the basis of population statistics and dispensations granted, material found in the National Archives (Riksarkivet). A slow increase is noted in the frequency of first-cousin marriages, from about 0.2 per cent in 1750 to about 1 per cent around 1800. Abrupt rise to the 1.5 per cent level after 1829; its probable causes.

6. Geographic, local differentiation of the frequency of first-cousin marriages in Sweden 1830–1844. The higher frequencies, around 2 per cent and above, are found in the north, west and south of the country. More or less continuous decrease, with lower frequencies around 1 per cent and below, towards the central eastern part of Sweden. During the period investigated, the different levels in respective parts of the country are fairly rigidly maintained. Underlying factors are briefly discussed, and some possibilities are mentioned.

7. A comparison is made (Table 3) between different districts (Dioceses) of Sweden with respect to the frequency of first-cousin marriages, population density, intensity of marriages occurring per 100 km², number of married persons per 100 km², and "isolate size" calculated according to *Dahlberg* (see p. 309). All figures are averages for the respective districts; their area in square kilometers is also given. The relevant figures make it reasonable to assume that practically all existing marriages within an area at a given time are renewed in about 25 years, this period then covering approximately one generation.

8. A high frequency of first-cousin marriage is found in the north of Sweden, in the least densely populated, forested region. Otherwise, no correlation is present between the level of the first-cousin marriage rate and population density and type of country, with respect to possible isolate "barriers". Instead, the differentiation follows the lines described under point 6, going straight across such differences as population density and topography, i.e., type of landscape. This fact should be borne in mind, even with due regard to possible variations within one and the same district.

9. In view of the relative constancy at different levels in various parts of the country, following the lines discussed under points 6 and 8, the following hypothesis is reasonable. A statistical relation may exist between the frequency of first-cousin marriages and certain demographic factors with a somewhat different action in various parts of the country, the latter systematic trend being a problem already discussed by *Sundbärg*. Consequently, it seems more reasonable to the present writer to assume

that some more "blindly" acting factors, of a population-statistical nature, are responsible for these often small differences, rather than more or less conscious traditions, socio-psychological in nature. Interpreted thus far, *Dahlberg* was correct.

10. It seems clear that such a relation is far from clear-cut, and may be fairly complex. It is possible that although the first-cousin marriage rates are of very special demographic interest, they are of subordinate importance from the purely genetic-statistical point of view. i.e.. with respect to the frequencies met with in human populations. They are difficult to evaluate with regard to isolating problems in human populations. the rigid isolate concept according to *Dahlberg and Wahlund* leading to oversimplification of actual fact.

11. Investigations of the frequency of first-cousin marriages in population samples from different rural districts of Sweden in recent times (*T. Sjögren; T. Larsson & T. Sjögren; J. A. Böök; C. A. Larsson.* and others) show close agreement with the results of the present investigation for the same parts of the country more than 100 years ago. This conservative feature is remarkable, in view of the greatly increased intermigration during the interval in question. It may afford additional support to the hypothesis put forward in point 9. and raise an objection to the "isolate" concept of *Dahlberg and Wahlund*.

12. Brief mention is made of *Cavalli-Sforza's* studies in the Diocese of Parma, Italy, on first-cousin marriage rates in villages of different size and altitude above sea level. The outbreeding effect due to non-occurrence of brother-sister matings is discussed with regard to panmictic conditions.

The contributions of *Bernstein* and his school in this respect are mentioned. Reference is made to *auf der Nöllenburg's* investigation of a closed population sample, an isolate in the true sense of the term.

13. The frequencies of first-cousin marriages have been calculated for a few districts (compartimenti) of Italy in recent times. as well as for Italy as a whole. The results somewhat resemble those found in Sweden for more than 100 years ago. i.e.. different rates are found in different parts of the country; locally they are fairly constant. at least over limited periods of time. The level seems to be independent of population density.

From about the beginning of the 20th century. a decrease in first-cousin marriages took place in Italy. with a minimum around the end of World War I. An increase followed. the same level having been reached nowadays as at the beginning of the century. Some local changes are discussed. e.g. a rise up to 1.7 per cent in Sicily. – These findings further stress the difficulty of evaluating first-cousin marriage frequencies when

estimating the isolate factors in human populations, where the distribution is more or less continuous. According to *Dahlberg*'s formula, the changes in the first-cousin marriage rate in Italy imply local variations in size of the hypothetical genetic isolates in a way which is unreasonable to assume.

Isolation by Distance, According to Sewall Wright, Studied in Human Populations

14. *Wright*'s method, i.e., the study of isolation by distance, seems more appropriate than that discussed above for investigations of human populations that are not closed, but are more or less continuously distributed.

15. For application of the method, the birthplaces of both parents and offspring must be known. *Wright*'s "neighbourhood" for a population within a given region is the area from which the parents may be presumed to be drawn "at random". It is defined as an area having a radius twice the standard deviation of the distance *in one direction* between parent-offspring birthplaces. The effective population size within this "neighbourhood" is calculated, and the ratio of the effective size of the total population of the country to that of the "neighbourhood" is computed.

16. The suitability is demonstrated of the old Swedish parish registers and vital statistics for a study of isolating factors by means of *Wright*'s approach. A brief account is given of four rural parishes, two in each of the counties of Östergötland and Västmanland, in different parts of central Sweden. The basic material consists of the series of marriages contracted in 1800–1824. The present paper is a preliminary report of a comprehensive investigation, covering the development in Sweden during the past 200 years. – The marriage-migration fields in the period now investigated clearly show the chief isolating factor to be that by distance. The majority of those marrying within a given area (parish) were born either within it or in a marginal zone around it.

In one parish, the migration field can be shown to have undergone fairly little change in the course of 150 years (1700–1849), only a slow increase being noted.

17. The more extensive investigation has two main purposes. Firstly, to ascertain the genetic-statistical background in a current study of the heredity and clinical features of schizophrenia and manic-depressive disorders in the county of Östergötland. Secondly, to try to obtain an idea of the dynamics of the gene flow in the whole country, problems inherent

in e.g. an earlier investigation of a rare, monohybrid recessive condition· (*Alström & Olson* 1957).

18. A survey of the calculations for the four rural parishes is given in Table 8. The effective population size in the three largest, forested parishes ranges from about 1,000 to 1,500 mating individuals. The smallest parish, of the plains type, has an effective population size in excess of 3,000. There is no reason to assume, in the regions investigated, a local random differentiation from the genetic-statistical point of view with respect to the total population.

The "isolation by distance" model for these four parishes is briefly compared with the "island" model approach, as well as with the results using *Dahlberg*'s "isolate" model. The superiority of the first-mentioned approach is emphasized, since it gives a full account not only of the crude migration, but also of the highly important migration fields.

19. A brief description is given of the basic material in a small town in central Sweden during the periods 1750–1774 and 1800–1824. The "neighbourhood" size is not calculated, since the material is not yet complete. It is nevertheless evident that this size will be far larger than that calculated for the rural parishes. It seems reasonable to assume that some small towns, at any rate, may serve as real "pacemakers" from the genetic-statistical point of view, within the rural backgrounds in which they are situated.

20. Due reservations are made for possible local random differentiation, especially in the less densely populated, northern part of the country. The importance is stressed of assembling such material, treated in an analogous way. This is now being done.

The Swedish Nobility as a Social "Isolate"

21. It seems reasonable to presume that, in earlier times, social barriers existed between the Swedish nobility and the remaining population, and were isolation factors of a more discontinuous nature. In this connexion, the "isolation by distance" model cannot be applied, the "island" model being more adequate.

22. As early as 1750–1759, the first-cousin marriage rate in the Swedish nobility as a social group was 3.5 per cent [Table 10, column (6)], about 10 times greater than that in the general population at the time.

23. Mention is made of *Fraccaro*'s paper, showing that the isolation by distance factor played a minor role for marriages *within* the nobility, as

compared to its effect in the general population, as studied in this paper.

24. Different mating combinations are computed for the Swedish nobility, with a division into high and low nobility, during 1680–1868. With the kind permission of *Sten Carlsson*, these calculations were made on his basic material (1949), taken from the works of *Elgenstierna* and of *Schlegel & Klingspor*.

25. Using material from the National Archives, the present writer has calculated the first-cousin marriage rates in the Swedish nobility and its substrata for the 1750–1844 period. Consistently high figures are found during the whole period, ranging from 3.5 per cent to over 6 per cent for the nobility as a social group: see Table 11, column (6).

26. Even higher frequencies, above 10 per cent, are found within each substratum, i.e., high and low nobility separately: see Table 11, columns (2) and (3). The figures are highest for the high nobility, at times even reaching about 13 per cent.

27. For the group of matings between purely noble partners in 1830 – 1839 – Table 11, column (5) – the mean coefficient of inbreeding can be computed at $F \sim 0.007$, with regard paid only to first-cousin marriages.

It is highly probable that, if more remote relationships could be taken into account, the mean coefficient of inbreeding for the high-noble group would be twice as high. The high nobility is the smallest subgroup, comprising about 150 matings per generation between high-noble men and high-noble women. It is also the most closed group as far as relations with the not-noble part of the population are concerned. Hence, the inbreeding effect can be assumed to be not negligible and, not to be forgotten, combined with an effect inherent in the limited size of the group.

28. The situation differs for the low nobility, despite the high degree of inbreeding there as well. This group is more open, and has a more intense connexion with the not-noble part of the population (Table 12). Its size is greater than that of the high nobility and, during the chief moulding time of the Swedish nobility – covering about 100 years from around 1650–1750 – its members were greatly incremented by recruitment from the not-noble population. About half the ennoblements took place from this time, and included both the men and their eventual families (Table 13). A positive selection with respect to the male elements must be assumed.

29. Somewhat less than half of the Swedish nobility is, however, of purely Swedish descent, the remainder originating from various parts of Europe. Consequently, there is reason to assume a not negligible heterosis effect during the moulding period at least in the low nobility.

30. Only 10 per cent of all ennoblements in the whole Swedish nobility occurred after the end of the 18th century. After the large influx of not-noble male elements during the moulding time, immigration of not-noble female elements into the low nobility by marriage assumed increasing importance. In 1700–1710, 22 per cent of low-noble men married not-noble women, the corresponding figure being 50 per cent in 1780–1789, and 74 per cent in 1860–1869 (Table 12). Thus, fairly intimate relations have consistently existed between the low nobility and the not-noble part of the population.

31. The high nobility was stressed to be the most closed subgroup (point 27), very few high-noble men mating with not-noble women in earlier times (Table 12). In fact, up to the middle of the 18th century, the majority of high-noble men married high-noble women. Later, however, not-noble elements were assimilated into the high nobility via matings of its men with low-noble women and then with not-noble women as well.

32. In point 30 was stressed the fairly intense and intimate relations between the low nobility and the not-noble part of the population, in contrast to the conditions in the high nobility. Consequently, the two former groups have been combined into one group with respect to females immigrating into the high nobility by marriage.

A schematic calculation is then made with a formula given by *Wahlund*. Some highly fictitious assumptions are made regarding the high nobility as an initially closed group – an "isolate" – subsequently broken down over the generations by exchange with the outside population. The proportions of exchange are given in Table 12. After seven generations, a difference inside-outside with respect to the frequency of a given autosomal gene has decreased to one-tenth of the original difference.

This is a maximum estimate. Deviations from the simplified assumptions still further decrease the difference as calculated above.

33. The high frequency of first-cousin marriages in the nobility compensates for the outbreeding effect due to the non-occurrence of brother-sister matings. It must be recalled that, in the beginning of the 18th century, a low first-cousin marriage rate, approaching zero, must be assumed even in the nobility, as in society as a whole. The reasons are given in point 4.

CONCLUSIONS

The relation between consanguineous matings and isolating mechanisms in human populations is briefly discussed. Two main sources of error with respect to different types of such mating are mentioned. (a) Matings between close relatives, including first cousins, do not occur at random; consequently, the figures are difficult to evaluate with regard to the so-called "isolate" size calculated according to *Dahlberg*. (b) Even if there is a greater probability that matings between more distant relatives occur at random, data on them are, as a rule, far from complete. The necessary genealogical checking of such data presents almost insurmountable difficulties.

The practically most important type of consanguineous mating is that between firstcousins; a brief study is therefore made of its geographic and demographic relations in Sweden in 1829–1844, as well as of the annual rate for the whole country since 1750. Some reasons for the lesser value of such frequency figures from the genetic-statistical point of view are discussed. Their importance is, in fact, of a more special, demographic nature in open, more or less continuously distributed, "natural" human populations. Despite a subsequent great increase in intermigration, subpopulations in different districts of Sweden in recent times have about the same first-cousin marriage rates as those found, in the present investigation, to exist in the same regions more than 100 years ago. Some support to the aforegoing hypothesis is given by the first-cousin marriage rates in Italy in recent times.

Reasons are given for the assumption that matings representing a degree of inbreeding as high as that between first cousins is of fairly recent date in Western societies, e.g. in Sweden, not until the beginning of the 18th century.

Sewall Wright's approach is briefly discussed as being most fruitful for a study of isolating factors even in human, "natural" populations. The chief such factor is "isolation by distance".

The "neighbourhood" area and its effective population size are computed for four small Swedish rural subpopulations (parishes) in 1800–1824.

The latter size is greatest in the smallest parish, i.e., about 3,000 mating individuals, the figures for the larger parishes being between 1,000 and 1,500. The smallest parish is of the plains type, the others are mixed agricultural and forest regions. With regard to the effective size of the total population as well, there seems to be no conclusive random differentiation within the regions investigated. An example is given of a small town which makes probable a "neighbourhood" far larger in size than those computed above. It seems reasonable to infer that such small towns may act as real "pacemakers" for the gene flow in the larger rural background in which they are situated.

Due reservations are made for the possibility of local random differentiation from the genetic-statistical point of view in certain other regions of the country, especially its northern part. Material is therefore being assembled from this region.

The importance is stressed of estimating the genetic-populational background along the lines of *Wright*, discussed above, when studying human hereditary conditions in a broader sense. The present writer is currently engaged in a genetic-clinical study of the major psychoses in the county of Östergötland, in central Sweden. In addition, an investigation is in progress regarding the spreading of a gene, the gene flow, in the population, problems inherent in an earlier study of a rare, monohybrid recessive condition.

A study is made of a social "isolate", the Swedish nobility, in the 1680–1868 period; it is based on *Carlsson*'s material from *Elgenstierna* and *Schlegel & Klingspor*. Using material from the National Archives, the frequencies of first-cousin marriages are computed for 1750–1844. The figures are consistently higher than in the general population; already in 1750–1759 the rate is 3.5 per cent as compared to 0.3 per cent in the general population, the corresponding figures in 1830–1839 being 6.1 and 1.4 per cent.

Even higher rates are found for such marriages in the two subgroups of the nobility, the high and low nobility; in the former they are at times as high as around 13 per cent, and in the latter in excess of 10 per cent. In the first subgroup at least, the rate approaches the level found among parents of patients with rare, monohybrid recessive diseases.

The two fractions of the nobility are analyzed separately. Despite the high degree of inbreeding, compensating for the outbreeding effect due to the non-occurrence of brother-sister matings, the low nobility in particular must be assumed to be highly heterogeneous, more than the general population. About 75 per cent of the nobility has been ennobled since

1644; at any rate in the low nobility, it is, in fact, reasonable to assume a not negligible heterosis effect during the moulding time of the nobility, from about 1650–1750. Less than half the nobility is of purely Swedish descent, the remainder originating from various parts of Europe. After this time, the influx of not-noble female elements through marriage is of increasing importance, and has an equalizing effect towards the not-noble part of the population.

Using a formula given by *Wahlund*, a calculation is made of the migration exchange in the high nobility, the smallest, most closed subgroup, with the highest degree of inbreeding. The gene difference inside-outside the group is found to have decreased in roughly seven generations since 1750 to one-tenth of the original difference. In actual fact, it is probably less, if some incorrect assumptions made for the purposes of simplification are disregarded.

It must be recalled that, at the beginning of the 18th century, the first-cousin marriage rate was approximately zero, both in the nobility and in society as a whole.

Résumé

Les relations entre mariages consanguins et les phénomènes d'isolement dans les populations humaines sont brièvement discutés. Deux principales sources d'erreurs concernant les différents types de mariages sont soulignées:

a) des mariages consanguins étroits, en particulier entre cousins germains, ne représentent pas un effet du hasard, par conséquent les chiffres sont difficiles à évaluer par rapport à la grandeur des isolats ("isolate size") selon la méthode de *Dahlberg;*

b) même s'il y a une plus grande probabilité que les mariages entre cousins éloignés soient dus au hasard, les informations sont, à ce sujet, loin d'être complètes. Les recherches généalogiques nécessaires pour ces indications présentent en général des difficultés presque insurmontables.

Le type le plus important des mariages consanguins est celui entre cousins germains. A ce sujet, des recherches géographiques et démographiques en Suède concernant la période 1829–1844 et la fréquence moyenne de ces mariages entre cousins germains pour tout le pays, depuis 1750, ont été faites. L'auteur discute la valeur moindre de ces derniers chiffres de fréquence du point de vue génétique et statistique. En effet, leur importance a plutôt une valeur démographique lorsqu'il s'agit de populations humaines

«naturelles» dont la distribution n'est pas entravée. Malgré une augmenta-
tion importante de l'intermigration des groupes de population dans diffé-
rentes régions de la Suède, le même taux de fréquence des mariages entre
cousins a été trouvé que celui d'il y a 100 ans. Des constatations analogues
concernant les mariages entre cousins germains ont été faites récemment
en Italie.

L'auteur expose les raisons qui font admettre que les unions du type
cousin germain sont de date assez récente dans les sociétés occidentales.

La conception de *Sewall Wright*, théorie la plus fructueuse pour l'étude
des facteurs isolants dans des populations humaines «naturelles», est briève-
ment discutée. Un des facteurs principaux est celui de «l'isolation par
distance».

Le «territoire de voisinage» et sa population effective sont évalués pour
quatre petites paroisses suédoises de 1800 à 1824. C'est ainsi que l'effectif
de la population de voisinage pour la paroisse la plus petite est le plus élevé,
comprenant environ 3000 individus en âge de se marier, alors que les
chiffres pour les paroisses plus grandes se situent entre 1000 et 1500 in-
dividus. La paroisse la plus petite est située en plaine, tandis que les
autres appartiennent à des contrées agricoles et forestières. En ce qui con-
cerne la grandeur effective de la population totale, il ne semble pas exister
de différentiation fortuite concluante dans les régions en question. Une
petite ville qui bénéficie d'un voisinage beaucoup plus étendu que ceux
mentionnés plus haut est citée en exemple. On peut admettre avec raison
que de telles petites villes jouent le rôle de véritables «entraîneurs» du flot
génique dans le large arrière-pays rural où elles sont situées.

Du point de vue génétique et statistique, il faut faire quelques réserves
quant à la possibilité d'une certaine différentiation fortuite locale dans
d'autres régions du comté, en particulier dans celles du nord. Une docu-
mentation a donc été rassemblée pour ces contrées septentrionales.

L'importance de l'estimation de la structure génétique de la population
selon la méthode de *Wright* exposée plus haut est soulignée pour l'étude
des conditions héréditaires humaines dans un sens plus large. L'auteur
procède actuellement à une enquête génétique et clinique des psychoses
principales dans le comté d'Östergötland en Suède centrale. En outre, une
investigations sur la diffusion d'un gène, le flot génique, dans la population
est en cours, problème qui se rattache à une étude préliminaire d'une affec-
tion récessive, monomérique rare.

Un «isolat social», la noblesse suédoise, a fait l'objet d'une étude por-
tant sur la période de 1680–1868; celle-ci se fonde sur le matériel de
Carlson provenant d'Elgenstierna et de *Schlegel & Klingspor*. En se basant

sur les Archives Nationales, les fréquences des mariages entre cousins germains ont été évaluées pour la période de 1750–1844. Les chiffres sont nettement plus élevés que pour la population générale; déjà pour la période de 1750–1759, le taux est 3.5% comparé à 0,3 dans la population générale; les chiffres correspondants pour la période de 1830–1839 sont 6,4% et 1,4% respectivement.

Des pourcentages même plus élevés ont été trouvés pour de tels mariages dans deux sous-groupes de la noblesse, la haute et la basse noblesse; dans la première, ils s'élèvent parfois à 13%, dans la seconde, ils dépassent 10%. Dans le premier sous-groupe au moins, le taux de consanguinité s'approche parfois de celui trouvé parmi les parents de cas avec des affections récessives monomériques rares.

Les deux fractions de la noblesse sont analysées séparément. Malgré le haut degré d'endogamie compensant l'effet exogamique dû à l'absence d'unions entre frères et sœurs, la basse noblesse doit, en particulier, être considérée comme très hétérogène. davantage que la population en général. Environ 75% de la noblesse a été annobli depuis 1644; de toute manière, on doit admettre, dans la basse noblesse, un effet d'hétérosis non négligeable pendant la période de formation de la noblesse, soit de 1650 à 1750 environ. Moins de la moitié de la noblesse est de pure origine suédoise, le reste provenant de diverses parties d'Europe. Après 1750, l'afflux d'éléments féminins n'appartenant pas à la noblesse, mais acquis par mariages, devient d'une importance croissante et tend vers un équilibre avec la partie de la population non noble.

En appliquant une formule établie par *Wahlund*, l'auteur calcule l'échange par migration dans la haute noblesse, ce sous-groupe très petit, très fermé et ayant le degré le plus élevé de consanguinité. La différence génique entre les taux à l'intérieur et à l'extérieur de ce groupe est tombée au cours de sept générations, depuis 1750, à un dixième de la différence initiale. En réalité, cette différence est probablement moins élevée, si l'on élimine quelques suppositions fausses faites en vue de simplification.

Mentionnons encore qu'au début du 18ème siècle, les mariages entre cousins germains étaient pour ainsi dire inexistants, aussi bien dans la noblesse que dans la société suédoise en général.

Zusammenfassung

Es wird die Beziehung zwischen Verwandtenehen und Mechanismen, die in menschlichen Bevölkerungen zur Isolatbildung führen, kurz dis-

kutiert, und es werden zwei Hauptfehlerquellen im Hinblick auf verschiedene Typen solcher Ehen erwähnt. a) Verbindungen zwischen nahen Verwandten, auch Vetternehen 1. Grades, sind nicht zufällig verteilt; infolgedessen ist es schwierig, die Daten auf die sogenannte «Isolatgröße» entsprechend der Berechnungsmethode von *Dahlberg* zu beziehen. b) Selbst wenn die Wahrscheinlichkeit größer sein sollte, daß Verbindungen zwischen entfernteren Verwandten zufällig verteilt sind, pflegen doch die darüber vorliegenden Daten von Vollständigkeit weit entfernt zu sein. Ihre notwendige genealogische Kontrolle bietet fast unüberwindliche Schwierigkeiten.

Der praktisch wichtigste Typ von Verwandtenehen ist die Vetternehe 1. Grades; deshalb wird sie in ihren geographischen und demographischen Aspekten in Schweden für den Zeitraum von 1829 bis 1844 kurz untersucht, und es wird die Gesamtzahl für das gesamte Land seit 1750 festgestellt. Es werden einige Gründe dafür angeführt, dass solche Häufigkeitsziffern vom genetischen Standpunkt aus einen geringeren Wert haben. In offenen, mehr oder weniger kontinuierlich verteilten, «natürlichen» menschlichen Bevölkerungen ist ihre Bedeutung tatsächlich mehr speziell-demographischer Natur. Trotz eines großen Anstieges der Binnenwanderung in der Zwischenzeit haben heutige Subpopulationen in verschiedenen Teilen Schwedens ungefähr die gleiche relative Anzahl von Vetternehen 1. Grades, die sich nach den hier vorgelegten Untersuchungen auch für die Zeit von vor mehr als hundert Jahren ergab. Die oben genannte Hypothese wird durch neuere Daten über Vetternehen 1. Grades in Italien gestützt.

Es besteht Grund zur Annahme, daß Verbindungen, die einen so hohen Grad von Inzucht repräsentieren wie eine Vetternehe 1. Grades, in westlichen Völkern erst in relativ neuer Zeit vorkommen, in Schweden z. B. erst seit Beginn des 18. Jahrhunderts.

Der Ansatz von *Sewall Wright* wird hervorgehoben als der ergiebigste für eine Untersuchung isolierender Faktoren auch in menschlichen, «natürlichen» Bevölkerungen. Der wichtigste Faktor ist die «Isolierung durch Distanz».

Der «Nachbarschaftsbereich» und seine wirksame Bevölkerungsgröße wird für vier kleine, ländliche schwedische Subpopulationen und für den Zeitraum 1800–1824 berechnet. Der letztgenannte Wert ist am höchsten in dem kleinsten Bereich, zirka 3000 Personen, die Kinder haben. In den größeren Bereichen liegt diese Ziffer zwischen 1000 und 1500. Der kleinste Bereich ist vom Ebenen-Typ, die anderen sind gemischte Acker- und Waldgebiete. Im Hinblick auf die wirksame Größe der Gesamtbevölkerung scheint innerhalb der untersuchten Gebiete keine sichere genetische

Differenzierung durch Zufallswirkungen zu bestehen. Es wird eine kleine Stadt als Beispiel genannt, welche wahrscheinlich eine wesentlich größere «Nachbarschaft» darstellt als die oben genannten. Es erscheint vernünftig anzunehmen, daß derartige kleine Städte tatsächlich als «Schrittmacher» des Genflusses für ihr ländliches Hinterland dienen. Es ist möglich, dass sich in anderen Teilen des Landes zufällig lokale genetische Unterschiede herausgebildet haben, besonders im Norden, und deshalb wird jetzt Material aus diesem Landesteil zusammengetragen.

Es wird die Bedeutung hervorgehoben, die einer Beurteilung des genetisch-bevölkerungskundlichen Hintergrundes nach den von *Wright* angegebenen Gesichtspunkten zukommt, wenn man erbliche Merkmale beim Menschen auf breiterer Basis erforschen will. Der Autor ist zurzeit mit einer genetisch-klinischen Untersuchung der wichtigeren Psychosen in der Provinz Östergötland (Zentralschweden) beschäftigt. Außerdem ist die Untersuchung über die Ausbreitung eines Gens, den Genfluß, in der Bevölkerung im Gange; das Problem ergab sich aus einer früheren Untersuchung über ein seltenes, einfach rezessives Merkmal.

Fernerhin wird ein soziales «Isolat», der schwedische Adel der Zeit von 1680–1868, auf Grund von *Carlssons* Material aus *Elgenstierna* und *Schlegel & Klingspor*, untersucht. Unter Benutzung von Material aus dem Nationalarchiv wird die Häufigkeit der Vetternehen 1. Grades für den Zeitraum von 1750–1844 errechnet. Sie ist wesentlich höher als in der allgemeinen Bevölkerung; schon zwischen 1750 und 1759 beträgt sie 3,5%, verglichen mit 0,3% in der sonstigen Bevölkerung, und für 1830 bis 1839 betragen die entsprechenden Zahlen 6,4 und 1,4%.

Noch höhere Ziffern finden sich in zwei Untergruppen des Adels, dem Hochadel und dem niederen Adel; in der ersten Gruppe liegen sie zeitweise sogar bei zirka 13%, in der zweiten über 10%. Mindestens in der ersten Gruppe nähert sich der Wert demjenigen, den man bei Eltern von Patienten mit seltenen rezessiven Erbleiden findet.

Die beiden Gruppen des Adels werden getrennt analysiert. Trotz des hohen Grades an Inzucht, der den durch das Fehlen von Bruder–Schwester-Verbindungen auftretenden Outbreeding-Effekt kompensiert, muß besonders der niedere Adel als sehr heterogen angesehen werden, mehr als die allgemeine Bevölkerung. Ungefähr 75% des Adels wurde seit 1644 geadelt; es ist tatsächlich vernünftig, wenigstens bei dem niederen Adel einen nicht zu vernachlässigenden Heterosis-Effekt während der Prägungszeit des Adels zwischen 1650 und 1750 anzunehmen. Weniger als die Hälfte des Adels ist rein schwedischer Abstammung; die übrigen stammen aus verschiedenen Teilen Europas. Nach dieser Zeit treten

immer mehr Frauen nichtadeliger Herkunft auf, die den Adel durch Heirat dem nichtadligen Teil der Bevölkerung angleichen.

Mit Hilfe einer von *Wahlund* angegebenen Formel wird der Wanderungsaustausch im Hochadel, der kleinsten, am meisten abgeschlossenen Untergruppe mit dem höchsten Grad von Inzucht, berechnet. Der Genunterschied zwischen dieser Gruppe und der Bevölkerung hat in den ungefähr 7 Generationen seit 1750 auf ungefähr einen Zehntel der ursprünglichen Differenz abgenommen. Tatsächlich ist er wahrscheinlich noch geringer, wenn man einige inkorrekte vereinfachende Annahmen beiseiteläßt.

Es muß daran erinnert werden, daß es zu Anfang des 18. Jahrhunderts fast keine, oder nur ausnahmsweise Vetternehen 1. Grades gab, weder beim Adel, noch in der Gesamtbevölkerung.

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Appendix 1. No. of first-cousin marriages and total no. of marriages contracted in Sweden 1750–1844.

Year	First-cousin	Total no. of	Year	First-cousin	Total no. of
	marriages			marriages	
1750	38	16,374	98	184	19,349
51	60	16,599	99	157	17,283
52	61	16,761	1800	134	17,528
53	45	15,923	01	142	17,057
54	45	17,457	02	197	18,500
55	57	17,097	03	175	19,491
56	55	16,005	04	168	19,335
57	52	15,078	05	138	20,197
58	49	15,273	06	189	19,492
59	48	18,529	07	204	19,959
1760	49	18,705	08	208	19,762
61	63	18,253	09	157	18,817
62	48	17,428	1810	228	25,780
63	69	16,850	11	227	25,615
64	54	17,219	12	216	22,054
65	69	16,066	13	192	18,745
66	72	16,419	14	220	18,281
67	70	16,539	15	262	23,553
68	66	17,039	16	265	23,069
69	50	16,463	17	235	20,938
1770	84	16,537	18	254	21,427
71	65	15,873	19	252	20,795
72	47	13,928	1820	241	21,722
73	72	15,560	21	267	22,890
74	80	17,433	22	263	24,431
75	69	19,002	23	251	23,993
76	91	18,310	24	248	23,907
77	78	18,577	25	248	23,640
78	93	18,692	26	216	22,525
79	95	18,035	27	183	20,339
1780	100	17,938	28	224	22,440
81	103	16,638	29	228	22,581
82	72	16,415	1830	291	22,222
83	89	17,124	31	296	19,983
84	105	16,031	32	284	20,935
85	117	16,791	33	312	23,029
86	96	17,297	34	303	23,803
87	137	17,253	35	336	22,533
88	127	17,235	36	358	21,816
89	106	17,369	37	314	21,153
1790	133	18,063	38	282	18,774
91	163	23,786	39	284	20,963
92	147	22,191	1840	353	22,071
93	117	19,934	41	348	22,619
94	124	18,509	42	311	22,691
95	132	17,279	43	328	23,167
96	158	19,747	44	356	24,208
97	183	19,523			

Appendix 2. Frequency of first-cousin marriages per annum 1839–1844 in different districts (Dioceses) of Sweden, listed from north to south.

District (Diocese)	1839			1840			1841			1842			1843			1844			Average %
	first-cousin marriages	total no. of marriages	%	first-cousin marriages	total no. of marriages	%	first-cousin marriages	total no. of marriages	%	first-cousin marriages	total no. of marriages	%	first-cousin marriages	total no. of marriages	%	first-cousin marriages	total no. of marriages	%	
1. Härnösand	39	1,412	2.8	35	1,472	2.4	47	1,811	2.6	49	1,813	2.7	40	1,957	2.0	52	1,923	2.7	2.5
2. Uppsala	29	2,100	1.4	32	2,283	1.4	29	2,271	1.3	23	2,209	1.0	26	2,224	1.2	27	2,182	1.2	1.3
3. Västerås	16	1,689	0.9	27	1,797	1.5	26	1,928	1.3	20	1,913	1.0	40	1,961	2.0	27	1,958	1.4	1.4
4. Karlstad	36	1,629	2.2	35	1,674	2.1	38	1,776	2.1	40	2,012	2.0	36	1,970	1.8	53	2,169	2.4	2.1
5. Göteborg	44	1,996	2.2	53	2,126	2.5	49	2,345	2.1	49	2,368	2.1	50	2,402	2.1	47	2,620	1.8	2.1
6. Skara	21	1,755	1.2	28	1,891	1.5	17	1,866	0.9	18	1,890	1.0	14	1,887	0.7	20	2,040	1.0	1.0
7. Strängnäs	11	1,464	0.8	10	1,570	0.6	21	1,527	1.4	9	1,550	0.6	13	1,604	0.8	14	1,656	0.8	0.8
8. Stockholm	3	607	0.5	7	583	1.2	6	643	0.9	2	611	0.3	4	616	0.6	2	661	0.3	0.6
9. Linköping	13	2,291	0.6	21	2,315	0.9	26	2,289	1.1	19	2,343	0.8	21	2,337	0.9	25	2,354	1.1	0.9
10. Växjö	16	1,531	1.0	24	1,599	1.5	17	1,546	1.1	19	1,543	1.2	19	1,649	1.2	18	1,681	1.1	1.2
11. Kalmar	5	796	0.6	9	881	1.0	5	863	0.6	6	829	0.7	5	835	0.6	7	859	0.8	0.7
12. Lund	42	3,432	1.2	70	3,604	1.9	54	3,460	1.6	54	3,309	1.6	52	3,403	1.5	51	3,794	1.3	1.5
13. Visby	9	261	3.4	2	276	0.7	13	285	4.6	3	295	1.0	8	322	2.5	13	311	4.2	2.7
Σ	284	20,963	1.4	353	22,071	1.6	348	22,610	1.5	311	22,685	1.4	328	23,167	1.4	356	24,208	1.5	1.5

LIBRI

A. E. Mourant, A. C. Kopec and *K. Domaniewska-Sobczak:* **The ABO Blood Groups.**
Comprehensive Tables and Maps of the World Distribution. Blackwell Scientific Publications, Oxford 1958. 276 p., 3 Tables and 6 Maps. 42 s.

In publishing this unique compilation, Dr Mourant has once more rendered invaluable service to research in human genetics and anthropology. In an easily reviewed, but nevertheless detailed tabular form, practically everything concerning ABO blood groups published prior to the conclusion of 1957 from all over the world is presented. The enormous number of investigations concerning the distribution of these blood groups compiled here reflects the increasing interest for human genetics, for the employment of blood groups in anthropology and, in addition, the increasingly more extensive employment of blood transfusions which has necessitated blood grouping of a great number of individuals. The volume must be described as a historical work as, for the first time, it is now possible to obtain a d e t a i l e d review concerning the distribution of the genes at an individual locus practically anywhere in the world. Since *Boyd* in 1939 published his standard work no attempt has been made to collect the accumulated information concerning the ABO locus. As a result of Dr Mourant's great interest for the subject and his extensive personal contacts with research workers concerned with this subject it has now proved possible to collect the colossal material which is of the greatest interest to all workers in human genetics and anthropologists, inter alia because many of the results published are personal communications or for other reasons not available in the original form. As a help in the evaluation of homogeneity and reliability the value is given for D σ for the ABO materials and for χ^2 for A_1A_2BO materials, the gene frequency being calculated here according to the maximum likelihood method.

It is stressed that it is difficult and will become even more so in future to delimit populations on account of the prevailing political conditions and the extensive migrations produced by such conditions to a not inconsiderable extent.

In addition to the Tables, maps are given of the distribution of the gene frequencies in Europe where future investigations will scarcely give rise to important changes in the broad outlines and also for the remainder of the world where the conditions have not yet been elucidated so clearly.

The authors express their wish to be kept up to date with new investigations of interest and to be informed of possible omissions from the material already published. This wish should be supported so that the valuable work presented here may retain the central position which it so rightly deserves. *Mogens Hauge, Copenhagen*